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PHYSIOLOGY OF GASTRIC SECRETION, PARTICULARLY AS RELATED TO THE ULCER PROBLEM

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The purpose of this paper is to present a brief review of certain aspects of the physiology of gastric secretion with the idea of indicating their actual or possible relation to the ulcer problem. No attempt will be made to list and evaluate the numerous theories of the genesis of ulcer.

The matter will be divided into three main sections. The first will deal with the normal physiology of stimulation and inhibition of gastric secretion and its composition and will contain a note regarding the normal control of gastric acidity. The second will deal with the abnormal factors which influence gastric secretion. The third will deal with gastric secretion as affected by ulcer and the relation of gastric juice to the causation of ulcer.

I. THE NORMAL PHYSIOLOGY OF GASTRIC SECRETION

The Interdigestive or Continuous Secretion, or the Interdigestive Period of Secretion.—The empty or fasting stomach usually secretes a small amount of gastric juice which is referred to as the interdigestive or continuous secretion. The normal rate of this secretion in man has been reported to be between 30 to 60 cc. per hour [1] and 15 to 117 cc. per hour.[2] Pavlov [3] denied the existence of continuous secretion and attributed such secretion as took place to psychic factors. It is difficult to deny this criticism absolutely; however, interdigestive secretion is known to occur in fasting with vagotomized pouches. Although the mechanisms concerned in its stimulation are obscure, its existence cannot be ignored.

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1. Ivy, A. C.: Surgery **10**:861, 1941.
2. Ihre, B.: Acta med. Scandinav., 1938, supp. 95, p. 1.
3. Pavlov, I. P.: The Work of the Digestive Glands, translated by W. H. Thompson, London, C. Griffin & Co., 1910.

There is some evidence that the mechanism of the interdigestive secretion may be disturbed in the patient with ulcer and may assume major proportions; this will be discussed later. Atropine, which normally abolishes this secretion, is not so effective in the presence of clinical and experimental ulcer.[4] On this basis, it has been suggested that irritated mucosa, like other irritated tissues (e. g., skin), produces histamine, since a histamine stimulus is the only one known which is not completely abolished by ordinary doses of atropine.[1]

The Gastric Secretory Response to a Meal—The Digestive Secretion—The Digestive Period of Secretion.—The digestive period of secretion is conveniently divided into three phases: the cephalic, the gastric and the intestinal. Each phase denotes the region in which the stimuli are acting to excite gastric secretion.

The cephalic phase is provoked by stimuli such as the thought, smell, sight or taste of food. These stimuli act in the presence of appetite through either conditioned (learned) or unconditioned (unlearned) reflexes. The vagi are the efferent nerves of the cephalic phase, since section of these nerves will abolish this phase of secretion; this phase can be abolished also by atropine. The gastric juice of the cephalic phase is highly acid and possesses considerable peptic activity. The amount of juice secreted during the cephalic phase in man is extremely variable, and its importance in the causation of ulcer is uncertain. This is due to several factors. First, the volume of secretion is affected by the appetite, the attitude of the subject, the type of food (agreeable or disagreeable), the time consumed in its ingestion, especially in the process of mastication, and the manner in which the food is prepared. Second, there is a lack of uniformity in the methods used by various investigators. No method of stimulating the cephalic phase or of determining the peptic activity of the juice has been generally accepted and employed. Since the cephalic phase is mediated by the vagi, it may be that the intravenous administration of insulin would give the most reproducible data for estimating the secretory potentiality of the vagi. Insulin provokes gastric secretion by the hypoglycemic stimulation of the vagal center. Ihre [2] made extensive use of this method and obtained about 140 cc. per hour from normal men. The cephalic phase, when studied by other methods, has given values of 50 to 150 cc. in twenty minutes.[1] Babkin [5] properly emphasized that the cephalic phase of secretion and the possibility that it may be exaggerated must not be neglected in any consideration dealing with the applied physiology of gastric secretion.

The gastric phase of secretion can be stimulated by mechanical distention and secretagogues. The secretagogues may be naturally

4. Keefer, C. S., and Bloomfield, A. L.: Effect of Atropine on Gastric Function in Man: Quantitative Study, Arch. Int. Med. **38**:303 (Sept.) 1926. Ivy.[1]

5. Babkin, B. P.: Canad. M. A. J. **38**:421, 1938.

present in the food or may arise as products of the digestion of food. Secretagogues may act per se or through the liberation of a gastric hormone. The exact mechanism of this stimulation of gastric secretion is uncertain. The vagi (preganglionic fibers) are not necessary for this phase of secretion. There are no satisfactory data regarding the volume of the gastric phase of secretion in man. The gastric phase of secretion will vary according to the time the food remains in the stomach, and this phase is still further complicated in the normal man by regurgitation and the overlapping of the intestinal and gastric phases of secretion. A more detailed review of this phase of gastric secretion may be found elsewhere.[6]

The intestinal phase of gastric secretion is provoked by the presence of secretagogues in the intestine. Mild distention of the intestine is without effect, and more serious distention inhibits gastric secretion. However, if the intestinal mucosa is injured, the release of histamine may stimulate gastric secretion. There are no data on the intestinal phase of gastric secretion in normal men. Garbat [7] obtained values of 120 to 170 cc. in two hours in patients with moderate gastric disorders.

The total volume of gastric secretion has been estimated at 2 to 3 liters per day,[8] but again there are no methods which give us exact data on man. The total volume of secretion is affected by the type of food ingested; for example, pure carbohydrates are much less potent stimuli than protein in the form of meat. Babkin [9] reviewed the literature dealing with the comparative potency of various foods as stimuli of gastric secretion.

The Inhibition of Gastric Secretion.—Two types of mechanisms are concerned in the normal inhibition of gastric secretion. First, there is nervous inhibition; both the vagi and the splanchnic nerves contain inhibitory fibers, and mental states may inhibit gastric secretion through these pathways. Distention of the intestine also inhibits gastric secretion, and this may take place reflexly. The second is humoral inhibition, in which the hormone enterogastrone is concerned. The normal mechanism for the release of enterogastrone is the presence of fat in the intestine. This hormone has been purified so that it may be administered intravenously or subcutaneously to dogs. It inhibits gastric secretion and motility.[10] Enterogastrone has been effective in preventing

6. Babkin, B. P.: Am. J. Digest. Dis. **1**:715, 1934. Necheles, H., in Portis, S. A.: Diseases of the Digestive System, Philadelphia, Lea & Febiger, 1941, p. 84. Ivy.[1]

7. Garbat, A. L.: Tr. Am. Gastro-Enterol. A., 1923, p. 45.

8. Rowntree, L. G.: Physiol. Rev. **2**:116, 1922.

9. Babkin, B. P.: Physiol. Rev. **8**:365, 1928.

10. Gray, J. S.; Bradley, W. B., and Ivy, A. C.: Am. J. Physiol. **118**:463, 1937.

the production of experimental gastrojejunal ulceration.[11] An effort to further purify the agent or agents responsible so that its use in man will be possible is at present being made.

Acid Inhibition.—Under certain conditions, acid (0.2 to 0.4 per cent) in the stomach or the duodenum inhibits gastric secretion. It is effective in the stomach in the presence of the gastric phase of secretion but not in the presence of the intestinal phase. Acid in the intestine inhibits the action of secretagogues in both the stomach and the intestine. If the stimulus for gastric secretion is sufficiently strong, acid will be ineffective. Acid inhibition fails also in the presence of the cephalic phase of secretion.[12] The inhibitory effects of acid appear to be due to a nervous rather than a humoral mechanism.

Substances in the Urine Which Affect the Stomach.—Sandweiss, Saltzstein and Farbman[13] were able to delay or prevent the production of experimental ulcer in dogs by the administration of extracts of human pregnancy urine and normal female urine. Further investigation of urinary extracts resulted in a preparation which inhibits gastric secretion and is free of pyrogenic impurities[14] and gonadotropic hormones.[15] The active principle which inhibits the secretion of acid was given the name urogastrone[14] to distinguish it from enterogastrone. Some evidence[16] has been obtained which indicates that the two substances (urogastrone and the substance of Sandweiss and associates) are not identical. It does not seem likely that urogastrone in its present state of purification would have much immediate practical value in the treatment of ulcer in man because of the large quantities of urine necessary for its manufacture. An attempt to evaluate urogastrone in the clinical treatment of ulcer will probably have to wait until the active principle has been isolated and chemically synthesized in large amounts. It is

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11. Hands, A. P.; Fauley, G. B.; Greengard, H., and Ivy, A. C.: Am. J. Physiol. **133**:P126, 1941.

12. Day, J. J., and Webster, D. R.: Am. J. Digest. Dis. **2**:527, 1935. Thomas, J. E.; Crider, J. O., and Mogan, C. O.: Am. J. Physiol. **108**:683, 1934. Wilhelmj, C. M.; McCarthy, H. H., and Hill, F. C.: ibid. **120**:619, 1937. Wilhelmj, C. M.; O'Brien, F. T., and Hill, F. C.: ibid. **115**:429, 1936.

13. Sandweiss, D. J.; Saltzstein, H. C., and Farbman, A.: Am. J. Digest. Dis. **5**:24, 1938; **6**:16, 1939.

14. Gray, J. S.; Culmer, C. U.; Wieczorowski, E., and Adkison, J. L.: Proc. Soc. Exper. Biol. & Med. **43**:225, 1940.

15. Culmer, C. U.; Atkinson, A. J., and Ivy, A. C.: Endocrinology **24**:631, 1939. Friedman, M. H. F.; Recknagel, R. O.; Sandweiss, D. J., and Patterson, T. L.: Proc. Soc. Exper. Biol. & Med. **41**:509, 1939. Gray, J. S.; Wieczorowski, E., and Ivy, A. C.: Science **89**:489, 1939.

16. Friedman, M. H. F.; Saltzstein, N. C., and Farbman, A.: Proc. Soc. Exper. Biol. & Med. **43**:181, 1940. Sandweiss, D. J., and Friedman, M. H. F.: Am. J. Digest. Dis. **7**:50, 1940. Wieczorowski, E.; Gray, J. S.; Culmer, C. U., and Wells, J. A.: Am. J. Physiol. **133**:P490, 1941.

not known what role, if any, urogastrone plays in the normal regulation of gastric secretion.

The Regulation of the Acidity of the Gastric Contents and Digestion.—The aforementioned factors play a role in the stimulation and inhibition of the volume output of secretion. The volume output of secretion and the rate of gastric evacuation are obviously concerned in the regulation of gastric acidity and digestion; in fact, we mention the point because these factors are frequently omitted from discussions of the regulation of the acidity of the gastric contents. It should be clear that as digestion proceeds, the stimulating effect of the food declines and the volume of secretion is accordingly diminished. Shortly after the meal has been ingested, the cephalic phase declines. Then, as the stomach empties, the gastric phase declines, and the secretagogues acting in the intestine are digested and absorbed. This is the chief cause of the rise and fall in the volume of secretion. Of course, such factors as enterogastrone, gastric emptying time and acid inhibition contribute to modify the character of the curve both qualitatively and quantitatively.

Factors other than the volume of gastric secretion and gastric evacuation operate to regulate the acidity of the gastric contents and its proteolytic activity. Three factors are chiefly concerned: 1. Food combines with, or "buffers," acid and pepsin; this in part explains the relief food affords to patients with ulcer. 2. The neutralization of acid and the inactivation of pepsin are brought about by the alkaline secretions. This process includes the slightly alkaline and diluting secretions of the stomach (mucous and mucoid secretion) and the regurgitation of bile, pancreatic juice and intestinal juice. 3. The products of peptic digestion per se inhibit peptic activity.

The Composition of Gastric Juice.—Normal gastric juice consists mainly of the following substances: hydrochloric acid, pepsin, mucin, inorganic salts, histamine, rennin, traces of lipase and an intrinsic factor which prevents pernicious anemia. The composition of the secretion from the different parts of the stomach varies according to the distribution of the various secretory cells in the stomach. Generally, the secretion of the cardia is alkaline and consists in great part of mucus; that of the fundus (this includes the fundus and the corpus according to anatomic terminology) is acid, and contains much pepsin and some mucus; the pyloric portion of the stomach secretes an alkaline mucus with no acid, but apparently the pylorus is important, though not essential, for the humoral phase of gastric secretion.[1]

Of all the constituents of gastric juice, acid has been most widely studied. This is due to two factors: first, the ease with which determinations may be made by titration with standard alkali, and, second, the fact that the secretion of acid may be provoked by an easily controlled stimulus—the subcutaneous injection of histamine. Vanzant

and co-workers [17] made an analysis of the normal range of acidity of the gastric contents after a test meal in almost 4,000 cases. The study of pepsin, however, is more difficult. There is no general agreement on the method of determining pepsin or the method of stimulating gastric juice with high peptic activity. Peptic activity depends principally on vagal activity, therefore drugs having effect on the parasympathetic system may be used; however, most of these drugs are inconvenient for general use because of their side reactions. Although the use of insulin appears to be the method of choice for stimulating the secretion of pepsin, it has not been used widely enough, and the hypoglycemic response of different subjects may be too variable to give standards of pepsin secretion such as are had for gastric acidity. The control and regulation of the various constituents of gastric juice have been described in detail by Babkin.[5]

II. ABNORMAL FACTORS WHICH INFLUENCE GASTRIC SECRETION

Organic Factors.—Acute gastric and duodenal ulcers have been produced by the administration of certain extracts of the posterior lobe of the pituitary gland [18] and by pitressin.[19] However, a reduction in the response to histamine has been observed after the injection of large amounts of posterior pituitary extract.[20] The experimental production of ulcer has been delayed or prevented by the administration of normal female or pregnancy urine extracts.[21] A decrease of 85 per cent in the acidity of gastric juice during pregnancy with return to normal values shortly after term has been observed.[22] This may have some relation to the infrequency of ulcer during pregnancy. Section of the pituitary stalk decreased the volume of gastric secretion,[23] but this may have been caused by the dehydration resulting from diabetes insipidus thus produced.

Ulceration of the gastrointestinal tract has been observed following adrenalectomy [24] and as a complicating factor in Addison's disease.[25]

17. Vanzant, F. R.; Alvarez, W. C.; Eusterman, G. B.; Dunn, H. L., and Berkson, J.: Normal Range of Gastric Acidity from Youth to Old Age: Analysis of 3,746 Records, Arch. Int. Med. **49**:345 (March) 1932.

18. Franchini, G.: Berl. klin. Wchnschr. **47**:613, 670 and 719, 1910.

19. Nedzel, A. J.: Experimental Gastric Ulcer (Pitressin Episodes), Arch. Path. **26**:988 (Nov.) 1938.

20. Hess, W. R., and Gundlack, R.: Arch. f. d. ges. Physiol. **185**:137, 1920.

21. Broad, G. G., and Berman, L. G.: Am. J. Digest. Dis. **8**:27, 1941. Sandweiss, Saltzstein and Farbman.[18]

22. Krahmer-Petersen, cited by Faber, K., in Kraus, F., and Brugsch, T.: Specielle Pathologie und Therapie, innere Krankheiten, Berlin, Urban & Schwarzenberg, 1914, vol. 5, p. 1015; cited by Ihre.[2]

23. Gross, E. G.; Ingram, W. R., and Fugo, N. W.: Am. J. Physiol. **133**: P118, 1941.

24. Mann, F. C.: J. Exper. Med. **23**:203, 1916.

25. Ask-Upmark, E.: Acta chir. Scandinav. **84**:55, 1940.

Hyperparathyroidism and hypercalcemia inhibited gastric secretion,[26] while hypocalcemia increased gastric secretion and diminished the concentration and total output of pepsin.[26c]

There are some indications in the literature that hepatic function is sometimes involved in the production of ulcer.[27] Gerez and Weiss [28] studied the relation of gastric secretion to hepatic function by observing the effects of an Eck fistula on the secretory response of a Pavlov pouch. There was an increase in the volume, the acidity and the duration of the secretion. It may be that this hypersecretion was produced because the liver did not remove the gastric secretagogues from the blood so quickly or efficiently as in the normal animal.

Nutritional Factors.—Since Pavlov's original investigations there has been no doubt that the volume and the composition of gastric secretion are related to the type of food ingested. Jarotsky [29] based his dietary treatment of peptic ulcer on the principles of the Pavlovian school. The present knowledge of nutrition has taught that there are factors other than secretagogues which are present in food and which may influence gastric secretion. Among these other factors are the vitamins. Unfortunately, most studies of the effect of vitamins on gastric secretion have dealt with avitaminosis almost to the exclusion of hypervitaminosis. In view of the modern tendency to "shotgun" vitamin therapy, especially in the hands of the layman, and the use of highly purified and concentrated vitamin preparations, it would seem desirable to increase the knowledge of the effects of hypervitaminosis on gastric secretion. It has been shown that the administration of irradiated ergosterol decreases gastric acidity in man and that the decrease is proportional to the amount of ergosterol used.[30] Deficiency of thiamine causes anorexia with concomitant decrease in the gastric secretion, and there are some indications that a deficiency of thiamine or the vitamin B complex may result in inflammation and ulceration of the gastrointestinal tract.[31] Deficiency of vitamin A has also been associated with a decrease in gastric acidity.[31] The significance of the food factor as related to the general nutritional state of the body was indicated by

26. (*a*) Babkin, B. P.: Rev. Gastroenterol. **7**:373, 1940. (*b*) Babkin, B. P.; Komarov, O., and Komarov, S. A.: Endocrinology **26**:703, 1940. (*c*) Schiffrin, M. J.: Am. J. Physiol. **135**:660, 1942.

27. Boles, R. S.; Riggs, H. E., and Griffiths, J. O.: Am. J. Digest. Dis. **6**:632, 1939. Bollman, J. L., and Mann, F. C.: Chronic Duodenal Ulcer in Animals with Eck Fistulas on Certain Diets, Arch. Path. **4**:492 (Oct.) 1927. Ask-Upmark.[25]

28. Gerez, L., and Weiss, A.: Ztschr. f. d. ges. exper. Med. **100**:281, 1937.

29. Jarotsky, A.: Acta med. Scandinav., 1930, supp. 35, p. 1.

30. Bauer, W.; Marble, A.; Maddock, S. J., and Wood, J. C.: Am. J. M. Sc. **181**:399, 1931.

31. Wilbur, D. L.: Am. J. Digest. Dis. **6**:610, 1939.

Mann,[32] McCarrison,[33] Fauley and Ivy[34] and Spira.[35] The different types of gastrointestinal lesions which seem related to some geographic factor[36] may in reality be due to the food habits prevalent in the locality, though this is entirely conjectural. Thus, Spira expressed the opinion that the familial incidence of ulcer (Hurst) also is caused by similar food habits. Secretagogues and vitamins, the type of food, how it is prepared and the mental state obtaining relative to its ingestion are not the only pertinent food factors. Every one who has worked with experimental gastric fistulas is well acquainted with the importance of maintaining an adequate mineral, salt and water intake. Deprivation of any of these factors will decrease gastric secretion. The importance of calcium was discussed by Gardner,[37] who made a study of functional disturbances of the gastrointestinal tract caused by a deficiency of calcium. Decker[38] produced acute ulcer in dogs by feeding hot (50 C.) gruel; however, the primary effect was congestion of the mucous membrane. The importance of fat in the normal mechanism of the humoral inhibition of gastric secretion has been indicated; therefore, it is of interest to note that a theory of the genesis of ulcer has been proposed[35] in which fat is supposedly the food factor responsible for the derangement of gastric function which produces ulceration!

Drugs.—Alcohol: Gastric secretion may be provoked by oral,[39] intraintestinal,[40] rectal[41] and intravenous[42] administration of alcohol. Dilue solutions (less than 15 per cent) stimulate a gastric secretion of high acidity and low peptic power.[43] It appears from indirect evidence

32. Mann, F. C.: Minnesota Med. **20**:755, 1937.

33. McCarrison, R.: Studies in Deficiency Diseases, London, Oxford University Press, 1921.

34. Fauley, G. B., and Ivy, A. C.: Experimental Gastric Ulcer: Effect of Consistency of Diet on Healing, Arch. Int. Med. **46**:524 (Sept.) 1930.

35. Spira, J. J.: The Causation of Chronic Gastro-Duodenal Ulcers, New York, Oxford University Press, 1931.

36. Walters, W.: Surg., Gynec. & Obst. **55**:355, 1932. Walters, W., and Sebening, W.: Minnesota Med. **15**:579, 1932.

37. Gardner, E. L.: Minnesota Med. **16**:698, 1933.

38. Decker, J.: Berl. klin. Wchnschr. **24**:369, 1887.

39. Cheney, W. F.: The Diagnosis and Treatment of Diseases of the Stomach and Intestines, in Christian, H. A.: Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1928, vol. 2.

40. Ivy, A. C., and McIlvain, G. B.: Am. J. Physiol. **67**:124, 1923. Cheney.[39]

41. Frouin, A., and Molinier, M.: Compt. rend. Acad. d. sc. **132**:1001, 1901. Radzikowski, C.: Arch. f. d. ges. Physiol. **84**:513, 1901.

42. Newman, H. W., and Mehrtens, H. G.: Proc. Soc. Exper. Biol. & Med. **30**:145, 1932. Petrovitch, A., and Bokanowa, E.: Compt. rend. Soc. de biol. **102**:633, 1929.

43. Babkin, B. P.: Die äussere Sekretion der Verdauungsdrüsen, ed. 2, in Gildemeister, M.; Goldschmidt, R.; Neuberg, C.; Parnas, J., and Ruhland, W.: Monographien aus der Gesamtgebiet der Physiologie der Pflanzen und der Tiere, Berlin, Julius Springer, 1928, vol. 15. Lönnquist, G.: Skandinav. Arch. f. Physiol. **18**:241, 1906.

that alcohol stimulates by causing the release of histamine from the tissues with which it comes in contact. High concentrations of alcohol irritate the gastric mucosa and provoke the secretion of mucus.[44] The prolonged administration of high concentrations may produce atrophic gastritis.[45] Obviously, alcohol is interdicted in the presence of ulcer by all physicians who believe that acid and irritants, such as alcohol, contribute to the chronicity of ulcer. It has been observed that the normal response of the secretion of mucus after the injection of pilocarpine nitrate is not seen in otherwise normal persons who habitually drink alcohol.[46] This indicates the presence of exhaustion of the mucous cells. The influence of alcohol on the digestive tract has been reviewed recently.[47]

Tobacco: Hurst and Stewart[48] expressed the opinion that the excessive use of tobacco is of greater importance in causing duodenal ulcer than in causing gastric ulcer. A large majority of their patients with duodenal ulcer smoked to excess; of course, many people without duodenal ulcer smoke to excess. Many clinical reports regarding the management of patients with ulcer recommend the interdiction of smoking. However, the literature on the effect of smoking on the acidity of the gastric contents after a test meal is at variance, though the majority of reports indicate an increase in acidity.[49] It should be emphasized that an increase in the acidity of the gastric contents does not necessarily mean that gastric secretion has been stimulated. It may mean that smoking caused some pylorospasm or decreased the motility of the stomach, each of which would cause some retention of the acid secreted. It may also mean a decrease in the secretion of mucus and the diluting secretion. If smoking actually and directly stimulates gastric secretion in a decisive way, as does a meal or a small dose of histamine, it is odd that smoking does not stimulate the secretion of the fasting stomach.[50] The observation that smoking does not definitely stimulate gastric secretion is not sufficient reason to countermand the interdiction against smoking for the patient with ulcer.

Some Other Drugs: Morphine increases gastric secretion after a transient period of inhibition.[51] The effect of morphine on the digestive

44. Barlow, O. W.: J. Pharm. **56**:117, 1936.

45. Thomsen, E.: Acta med. Scandinav. **61**:522, 1925.

46. Necheles, H., and Coyne, A.: Secretion of Mucus and Acid by Stomach in Healthy Persons and in Persons with Peptic Ulcer, Arch. Int. Med. **55**:395 (March) 1935.

47. Beazell, J. M., and Ivy, A. C.: Quart. J. Stud. on Alcohol **1**:45, 1940.

48. Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcer, New York, Oxford University Press, 1929.

49. Ehrenfeld, A. B., and Sturtevant, M.: Am. J. M. Sc. **201**:81, 1941.

50. Schnedorf, J. G., and Ivy, A. C.: Effect of Tobacco Smoking on Alimentary Tract: Experimental Study of Man and Animals, J. A. M. A. **112**:898 (March 11) 1939.

51. Riegel, F.: Ztschr. f. klin. Med. **40**:347, 1900.

tract has been reviewed by Krueger.[52] Sulfanilamide depresses gastric secretion.[53] The histamine antagonist thymoxyethyldiethylamine does not affect the gastric response to histamine.[54]

Psychic Factors.—The importance of the emotions in their relation to gastric function is a matter of common observation. Descriptions of the patient with ulcer usually include such characteristics as "high strung, nervous, worrying, aggressive, go-getter." This subject has been reviewed elsewhere.[55] Alexander [56] presented a speculative discussion of this subject from a psychiatric viewpoint. In the dog and in most human subjects, an emotional insult causes depression of the gastric secretion and motility. The report of Wittkower [57] is of special significance. His observations of human subjects indicated that emotions, such as fear, disgust and joy, did not always produce the same effect on gastric secretion. However, each person manifested a characteristic response, that is, an increase or a decrease of gastric secretion. This suggested that some inherent nervous or psychiatric factor predisposes to hypersecretion in the presence of emotional stimuli. This recalls Todd's observations regarding the effect of anxiety and stress on the motor activity of the stomachs of medical students. In the majority of students emotional states continued, after repeated exposure, to cause inhibition of the stomach. In a few subjects, however, who responded to stress by the manifestation of outward poise but with internal tension, the stomach became tonic and hypermotile. It was in the latter group that duodenal ulcer appeared when it appeared during the medical course. Ask-Upmark [25] observed a high incidence of ulcer among those "doing service behind the enemy lines" in the Russian-Finnish war. It is not unlikely that the heightened nervous tension of modern warfare will make peptic ulcer a major problem among the armed forces. Hurst [58] presented his experiences to date in the present war.

Effect of Surgical Procedures.—Vagotomy will abolish the cephalic phase of gastric secretion and consequently reduce the total volume of secretion in the response to a meal. For this reason, its value (in conjunction with other operative procedures) has been considered.[59]

52. Krueger, H.: Physiol. Rev. **17**:618, 1937.

53. Davenport, H. W.: Am. J. Physiol. **133**:P69, 1941.

54. Chickering, O., and Loew, E. R.: Am. J. Physiol. **133**:P51, 1941.

55. (*a*) Alvarez, W. C.: Nervous Indigestion, New York, Paul B. Hoeber, Inc., 1930; Am. J. Surg. **18**:207, 1932. (*b*) Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916; Physiol. Rev. **3**:1, 1923. (*c*) Eusterman, G. B., and Balfour, D. C.: The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1935.

56. Alexander, F., in Portis, S. A.: Diseases of the Digestive System, Philadelphia, Lea & Febiger, 1941.

57. Wittkower, E.: J. Ment. Sc. **81**:533, 1935.

58. Hurst, A. F.: Am. J. Digest. Dis. **8**:321, 1941.

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Obviously, the success of vagotomy in the treatment of ulcer will depend on the relative importance of the cephalic phase or vagal activity before operation and on the factors occurring as a result of vagotomy which may influence gastric secretion. It has been demonstrated that the vagi are necessary for the maintenance of normal gastric tone and that the rate of the evacuation of some foods from the stomach is retarded by vagotomy.[60] The prolonged presence of food in the stomach, unless this is prevented by an additional operation, will increase the gastric phase of secretion and thus tend to defeat the original purpose of vagotomy. Since vagal stimulation produces vasodilation of the blood vessels of the stomach,[61] vagotomy might decrease, at least temporarily, the blood supply to the gastric and the intestinal mucosa owing to the unopposed constrictor activity of the splanchnic nerves.

The gastric phase of secretion can be reduced by gastroenterostomy, provided this procedure decreases the gastric emptying time and the intragastric tension. The operation favors also the regurgitation of the alkaline duodenal contents. On theoretic grounds this operative procedure is most likely to be of value in the presence of high grade pyloric achalasia or stenosis and a stomach that does not secrete acid excessively. In dogs, gastroenterostomy cannot be relied on to decrease gastric secretion either in the presence or the absence of partial pyloric stenosis.[62] Matthews and Dragstedt [63] demonstrated experimentally the importance of the regurgitation of the alkaline duodenal contents. When a valve which prevented regurgitation was placed in the pylorus, the healing time of experimentally produced gastric ulcers was often delayed to twice that required when normal regurgitation took place. McCann [64] made an extensive study of the effects of various types of enterostomy on experimental animals. Gastroenterostomy seems to be contraindicated in the presence of true hypersecretion, since it does not attack the cause of the secretion and exposes the vulnerable jejunum to the proteolytic action of the gastric juice.

Subtotal gastrectomy is performed so that regurgitation may occur more readily, the emptying time of the stomach may be reduced, the

59. Best, R. R., and Orator, V.: Ann. Surg. **96**:184, 1932. Klein, E.: Gastric Secretion After Partial Gastrectomy, J. A. M. A. **89**:1235 (Oct. 8) 1927; Ann. Surg. **90**:65, 1929. Shapiro, P. F., and Berg, B. N.: Return of Gastric Acidity After Subtotal Gastrectomy and Double Vagotomy, Arch. Surg. **28**:160 (Jan.) 1934. Winklestein, A., and Berg, A. A.: Am. J. Digest. Dis. **5**:497, 1938.

60. Meek, W. J., and Herrin, R. C.: Am. J. Physiol. **109**:221, 1934.

61. Stahnke, E.: Arch. f. klin. Chir. **132**:1, 1924. Vineberg, A. M.: Ph.D. Thesis, McGill University Graduate School, Montreal, 1933, p. 53.

62. Medoff, J.; Neuwelt, F.; Ptedjl, J., and Necheles, H.: Am. J. Physiol. **133**:386, 1941.

63. Matthews, W. B., and Dragstedt, L. R.: Surg., Gynec. & Obst. **55**:265, 1932.

64. McCann, J. C.: Experimental Peptic Ulcer, Arch. Surg. **19**:600 (Oct.) 1929.

ulcer-bearing area may be excised, part of the humoral mechanism of gastric secretion may be removed and some of the acid-secreting area may be excised. Recently, Lewis [65] excised the mucosa of the pyloric antrum and observed a decrease in the volume of secretion. This indicates the importance of the pyloric mucosa. More recently,[1] evidence has been obtained which indicates that the pyloric mucosa contributes to, but is not the sole origin of, the humoral mechanism of gastric secretion. Connell [66] made use of a subtotal gastrectomy, fundusectomy, which removes most of the acid-secreting area of the stomach. Wangensteen [67] also employed this procedure and found, as might be expected, a high incidence of anacidity, at least for a number of months after the operation.

It is certain that partial gastrectomy will reduce the gastric phase of secretion. The extent to which this takes place will depend chiefly on the extent to which the acid-secreting area has been resected and on the eventual degree of hypertrophy and hyperplasia of the gastric remnant. The degree of hypertrophy may depend on the rate of emptying of the remnant and the size and the character of the meal.[1] Attempts to correlate the acidity of the gastric contents with the clinical results following subtotal gastrectomy were not uniformly attended with success according to a more recent report.[68] This is not surprising in view of the manifold factors which are operating before and after partial gastrectomy in the patient with ulcer.

Other Factors.—Roentgen rays [69] and fever [70] depress gastric secretion. A decrease in the red blood cell count [71] and anoxemia [72] reduce gastric acidity. Cholecystitis and cholelithiasis do not uniformly or characteristically affect gastric acidity.[73] Burns produce hypersecretion.[74] There is no apparent relation between gastric acidity and height

65. Lewis, E. B.: Surgery **4**:692, 1938.

66. Connell, F. G.: Surg., Gynec. & Obst. **49**:696, 1929; Ann. Surg. **96**:200, 1932.

67. Wangensteen, O. H.: Surg., Gynec. & Obst. **70**:59, 1940.

68. Strauss, A. A.; Strauss, S.; Levitsky, P.; Sheman, L.; Seidman, E. E.; Arens, R. A., and Meyer, J.: Am. J. Digest. Dis. **4**:32, 1937.

69. Portis, S. A., and Arens, R.: Am. J. Roentgenol. **11**:272, 1924. Palmer, W. L., and Templeton, F.: Effect of Radiation Therapy on Gastric Secretion, J. A. M. A. **112**:1429 (April 15) 1939. Snell, A. M., and Bollman, J. L.: Am. J. Digest. Dis. **1**:164, 1934.

70. Meyer, J.; Cohen, S. J., and Carlson, A. J.: Gastric Secretion in Fever, Arch. Int. Med. **21**:354 (March) 1918.

71. Apperly, F. L., and Cary, M. K.: Am. J. Digest. Dis. **3**:466, 1936.

72. Pickett, A. C., and Van Liere, E. J.: Am. J. Physiol. **123**:163, 1938.

73. Sagal, Z.; Marks, J. A., and Kantor, J. L.: Ann. Int. Med. **7**:76, 1933. Vanzant, F. R.; Alvarez, W. C.; Berkson, J., and Eusterman, G. B.: Changes in Gastric Acidity in Peptic Ulcer, Cholecystitis and Other Diseases Analyzed with Help of New and Accurate Technique, Arch. Int. Med. **52**:616 (Oct.) 1933.

74. Necheles, H., and Olson, W. H.: Am. J. Physiol. **133**:396, 1941.

and weight in man.[75] Brunschwig and associates [76] reported that the intravenous injection of an extract of the gastric juice of patients with either pernicious anemia or gastric carcinoma inhibits the gastric secretion in dogs.

III. GASTRIC SECRETION IN THE PRESENCE OF ULCER AND ITS RELATION TO THE CAUSATION OF ULCER

Gastric Secretion in the Presence of Ulcer.—Sagal, Marks and Kantor [73] studied the clinical significance of the acidity of the gastric contents in patients with digestive symptoms. A modified Boas-Ewald test meal was used, and a table of standard values of the secretory response was prepared. Acid values higher than those usually found in normal subjects were common in the presence of ulcer, particularly duodenal ulcer. Hypersecretion of the interdigestive phase has been observed with duodenal ulcer.[77] This is in agreement with the earlier work of Dragstedt and Vaughn,[78] who demonstrated an increase in the secretion of a Pavlov pouch in the presence of experimental ulcer. Necheles and Maskin [79] reported an increase in the cephalic phase of secretion in patients with ulcer. However, they stated their belief that this is not a major factor in the genesis of ulcer. This view is not in agreement with that of Babkin [5] and Winkelstein,[80] who expressed the opinion that the vagus may play an important role in the genesis of ulcer. This is supported by Cushing's [81] observations of various types of ulcer in the presence of lesions of the midbrain, although the occurrence of ulcer under such conditions is not a uniform experimental finding.

Ihre [2] made an extensive study of the effects of ulceration on gastric secretion in man. Analysis was made of the fasting secretion and that provoked by histamine and insulin. Some of his data have been recalculated and are presented in the table.

The volume of secretion was not materially affected by gastric ulceration; however, in the presence of duodenal ulcer, the three types of secretion were greater than normal. Gastritis, uncomplicated by

75. Vanzant, F. R.; Alvarez, W. C., and Berkson, J.: Am. J. Digest. Dis. **3**:83, 1936.

76. Brunschwig, A.; Clarke, T. H.; Van Prohaska, J., and Schmitz, R. L.: Surg., Gynec. & Obst. **70**:25, 1940. Brunschwig, A.; Van Prohaska, J.; Clarke, T. H., and Kandel, E.: J. Clin. Investigation **18**:415, 1939.

77. Bloomfield, A. L.; Chen, C. K., and French, L. R.: J. Clin. Investigation **19**:863, 1940.

78. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, Arch. Surg. **8**:791 (May) 1924.

79. Necheles, H., and Maskin, M. H.: Am. J. Digest. Dis. **3**:90, 1936.

80. Winkelstein, A.: Am. J. M. Sc. **185**:695, 1933; New York State J. Med. **37**:1989, 1937.

81. Cushing, H.: Surg., Gynec. & Obst. **55**:1, 1932.

ulcer, showed hyposecretory responses. The hypersecretion associated with duodenal ulcer and the normal secretion associated with gastric ulcer have been observed by others. However, there is no satisfactory explanation of this phenomenon. The failure of atropine to abolish the interdigestive secretion in duodenal ulcer has been taken as evidence that histamine or some histamine-like substance may be responsible for the secretion.[1] A histamine cycle has been suggested in which the irritated mucosa liberates histamine which in turn stimulates gastric secretion; the action of the gastric juice on the ulcer liberates more histamine, and thus the cycle continues. This might explain the hypersecretion of the fasting state in duodenal ulcer, but why does not gastric ulcer produce the same effect? Is it not possible that gastric ulcer, too, might liberate histamine? The presence of gastritis involving the acid-secreting mucosa might be involved; this would reduce the secretory response to excitants.

Ulceration may act also in other ways to influence the gastric secretion and the acidity of the gastric contents. The emptying time of the

Effects of Ulcer on the Gastric Secretion of Human Beings

Condition	Average Volume of Response; Percentage of Normal		
	Fasting	Histamine	Insulin
Gastric ulcer	100	100	120
Duodenal ulcer	170	155	141
Gastritis (without ulcer)	69	58	54

stomach is delayed in some patients in the presence of ulcer,[82] and this tends to increase the gastric phase of secretion. The production of mucus is also impaired, at least in relation to the production of acid, in patients with ulcer,[46] and this might increase the acidity of the gastric juice. There are some indications in the literature of a tendency of the acidity of the gastric contents to diminish as the ulcer enters a remission under management. Brown and Dolkart [83] reported that gastric acidity tends to moderate as the gastrointestinal tract returns to normal, but they were not able to observe any significant trend in the gastric acidity prior to a recurrence of ulcer activity.

Relation of Gastric Secretion to the Causation of Ulcer.—There are many mechanisms which may be concerned in the production of the primary defect in the stomach or the duodenum, but why this defect sometimes develops into an ulcer and other times heals spontaneously is uncertain. One thing is certain—the actual destruction of the tissue results from the proteolytic (hydrochloric acid and pepsin) action of the

82. Ivy, A. C.: Physiology of the Stomach: Studies on Gastric Ulcer, Arch. Int. Med. **25**:6 (Jan.) 1920.

83. Brown, C. F. G., and Dolkart, R. E.: Gastric Acid During Recurrences and Remissions of Duodenal Ulcer, Arch. Int. Med. **60**:680 (Oct.) 1937.

gastric juice. A large amount of experimental evidence has shown that the corrosive action of gastric juice is of prime importance in the genesis of postoperative jejunal ulcer and that gastric juice is undoubtedly a chronicity factor in delaying the healing of experimental gastric lesions.

Much emphasis has been placed on the acidity of the gastric juice without regard to peptic activity. Mann [83a] expressed the opinion that the importance of acid in the causation of ulcer cannot be overemphasized. The fact that ulcer has been produced by a technic which allows for the continuous absorption of histamine [84] has been used to strengthen the supposition that acid is the cause of ulcer; however, histamine juice contains ample pepsin. The role of acid per se has been emphasized by Dragstedt.[85] The large accumulation of clinical evidence showing the beneficial effects of neutralization and buffering substances also has served to emphasize the importance of acid. Yet the proteolytic power of gastric juice is due not to acid alone, but to pepsin in acid solution. The difference in the irritating properties of acid and acid and pepsin has been demonstrated recently by experiments in which loops of jejunum were perfused with either acid or acid and pepsin.[86] Bleeding or ulceration were never produced by the concentration of acid used, while ulceration always followed the perfusion when pepsin was added to the acid. As a matter of fact, ulceration of the gastrointestinal tract has never been produced by physiologic concentrations of acid in the complete absence of pepsin. That pepsin may play a significant role is further indicated by the high incidence of hyperpepsinia in connection with duodenal ulcer.[2] It seems desirable to use some therapeutic agent that will neutralize acid and be able to inactivate pepsin. Some aluminum compounds have these properties.[87]

In conclusion, it should be stated that this discussion of the physiology of gastric secretion and the relation of hydrochloric acid and pepsin to the problem of ulcer is not intended to imply that the excessive secretion of gastric juice or its retention in the stomach is the cause of gastroduodenal ulcer. It is our opinion, based on our own studies and the evidence in the literature, that the irritating action of acid and pepsin is the prime factor in the genesis of postoperative jejunal ulcer and is an important factor in the development, persistence and perforation of gastric or duodenal ulcer.

83a. Mann, F. C., in Eusterman and Balfour.[55c]

84. Varco, R. L.; Code, C. F.; Walpole, S. H., and Wangensteen, O. H.: Am. J. Physiol. **133**:P287, 1941.

85. Dragstedt, L. R., and Matthews, W. B.: Am. J. Physiol. **105**:29, 1933.

86. Schiffrin, M. J.: Proc. Soc. Exper. Biol. & Med. **45**:592, 1940. Schiffrin, M. J., and Warren, A. A.: Am. J. Physiol. **133**:P437, 1941; Am. J. Digest. Dis., to be published.

87. Komarov, S. A., and Komarov, O.: Am. J. Digest. Dis. **7**:166, 1940. Schiffrin, M. J., and Komarov, S. A.: ibid. **8**:215, 1941.

MOTOR PHYSIOLOGY OF THE STOMACH, THE PYLORUS AND THE DUODENUM

WITH SPECIAL REFERENCE TO GASTRODUODENAL ULCER

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Numerous experimental methods are known which lead to ulceration of the stomach. Of these methods, the greatest significance is attached to those employed by Exalto, Mann, Ivy, Dragstedt and others, who produced chronic peptic ulcer by experimental alterations in gastrointestinal function. The ulcer thus produced resembles grossly and histologically the clinical lesion, and both respond in a similar manner to therapy. From such studies more is already known regarding the basic factors causing or curing the experimental lesion than those influencing the spontaneous ulcer, and the information available with respect to both lesions exceeds that regarding ulcer in other and frequently more accessible portions of the body.

The studies on experimentally produced ulcers have greatly revived interest in the fundamental ulcer problems—why ulcers form, become chronic, undergo hemorrhage or perforate and how they can be prevented or healed. So far, the investigations have been most fruitful in establishing the fundamental alterations in gastrointestinal function which are essential in the genesis of this condition. Since such knowledge may be considered a prerequisite to an ultimate solution of the problems involved, satisfactory forward strides appear imminent, and attainment of the goal does not appear impossible.

As yet, no specific cause or therapy of the chronic clinical condition has been established from experimental or clinical observations. The divergence in the teachings among outstanding clinicians regarding what constitutes the therapy of choice for ulcer and the avidity with which new therapeutic procedures are greeted constitute adequate comment on the present status. However, the physiologic method of approach to this problem has been gradually replacing empiricism and has placed the investigations on a more satisfactory scientific level. While the mode of attack was limited to empiric methods, much valuable information accrued, but such studies were so handicapped by an inability adequately to control or check many essential aspects and to distinguish objective results from subjective impressions that forward steps were

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necessarily slow and uncertain. The most significant progress can be anticipated when clinical observations and animal studies by competent investigators are carefully integrated and correlated so that each can act both as an inspiration and as a check on the other.

Among the methods of producing experimental ulcer, the procedures which simulate most closely the clinical conditions are those involving extensive mechanical and chemical trauma to the digestive tract. The major emphasis has been placed on gastric acidity, but ulcer does not develop in all cases of hyperacidity, and ulcer may heal in the presence of hyperacidity. Apparently acidity is only one of the factors involved. An important role is also played by the motor activities of the intestine, especially those involving spasm, hypermotility and atonia. Thus the physiologic factors developing the propulsive force, resulting from the force with which food is propelled, or those causing stagnation require special emphasis. It is the purpose of this report to relate to the ulcer problem the normal and abnormal manifestations of these motor activities.

Clinically, peptic ulcer develops chiefly in the distal part of the esophagus, the stomach and the proximal part of the duodenum. These organs have as a common function the transportation of food, and in the esophagus and the duodenum this propulsion is the paramount motor function. In addition to propulsion, the stomach has the important motor task to store food, to break it up into fragments and to mix it with gastric juice. Further, there are certain movements of the esophagus, the stomach and the duodenum designated as hunger contractions which have the important function of initiating hunger sensations and thus apprising the subject that realimentation is desirable.

HUNGER AND APPETITE

The intake of food is normally accurately related to the metabolic needs of the person. This is evidenced by the fact that the body weight of an adult remains relatively constant over extended intervals in spite of considerable variations in metabolic requirements. So well is this fact recognized that sudden changes in body weight are considered with suspicion by both the patient and the clinician. On the other hand, the growing child, the convalescent patient, the person performing heavy manual labor or the pregnant woman all require a relative increase in caloric intake, and in such persons the subjective demand for food likewise parallels the need.

The factors involved in the regulation of the intake of food and its correlation with metabolic needs are important and have been extensively investigated. The regulation is achieved through the sensations of appetite and hunger. In a broad sense, these are considered as the sum total of the conditions determining the ingestion of food. Since they

persist during the entire span of life of the subject and may exert a predominant control over his activities, they constitute the most potent influence in life. The entire behavior of man and animals is fundamentally related to the preservation of the life of the individual and the perpetuation of the species. This behavior may be resolved into the activities related to satisfying the demands for food, water, salt and sex gratification. Normally these activities are modified by training and culture, but this veneer is readily hidden under circumstances which release from confinement the powerful driving forces which constitute the fundamental urges. The behavior of the members of the Donner party in 1846-1847 when misfortune interrupted their migration to California may be considered as a demonstration of the force of primitive hunger. "The horror of these people eating each other's brains, entrails, legs and other tissues is scarcely less than the horror of the callous and grasping way in which some of them behaved in the face of starvation."

Hunger is an unpleasant sensation of emptiness, gnawing tension and discomfort or dull pain in the epigastric region. A feeling of lassitude, weakness, faintness, headache or nausea may also be present and may even dominate the picture. There is a general increase in irritability of the central nervous system and vasomotor instability. Cannon,[1] Carlson [2] and their students have been particularly active in demonstrating that the sensation of hunger results directly from peculiar movements (hunger contractions) occurring in the lower part of the esophagus, the stomach and the duodenum. These contractions initiate impulses which are carried over the vagi to the medulla where they affect respiratory and cardiovascular centers, then pass to the midbrain and the thalamus, where they are appreciated as rather generalized, crude or protopathic sensations. However, there is some localization to the epigastrium, and a trained person can distinguish between gastric and duodenal contractions.[3] A similar localization of pain from faradic stimulation of the stomach or the duodenum of human subjects was noted by Boyden.[4]

Animals appear to experience hunger after extirpation of the stomach, denervation of the stomach and also after vagotomy, splanchnicotomy and celiac ganglionectomy. This and other related evidence

1. Cannon, W. B.: The Mechanical Factors of Digestion, London, E. Arnold, 1911; Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton and Company, 1915.

2. Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916.

3. Quigley, J. P., and Solomon, E. I.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: V. (*a*) Action on the Human Duodenum; (*b*) Action on the Colon of Dogs, Am. J. Physiol. **91**:488 (Jan.) 1930.

4. Boyden, E. A., and Rigler, L. G.: Localized Pain Accompanying Faradic Excitation of the Stomach and Duodenum, Proc. Soc. Exper. Biol. & Med. **31**:655 (March) 1934.

suggests that a mechanism, probably centrally located, in addition to the hunger contractions produces the hunger sense and behavior in the normal person.[5]

Appetite is a cerebral phenomenon, a conditioned reflex developed largely on previous feeding experiences which caused the disappearance of the hunger distress and its replacement by a feeling of well-being. Appetite is also based on the agreeable smell, the taste and the appearance of food, on habit and many other factors and in general is a pleasant experience. In the normal civilized person having three meals daily, the ingestion of food is dependent chiefly on habit and appetite.

Hunger is especially important in the infant before appetite has developed. It produces restlessness, causes the infant to attempt to eat many substances and by experience to learn what and how to eat and finally to develop appetite. Richter's[6] experiments were illustrative in this respect, for he found that the physical activity of rats was greatest during the hunger period but that after eating they fell asleep.

Hunger contractions develop in the empty stomach at a variable interval after gastric emptying. This latent period, the vigor of contractions and the relative duration of hunger and rest periods are usually directly related to the metabolic needs of the subject (age, length of fast, metabolic rate, etc.). Usually a thirty to forty-five minute period of activity alternates with a thirty to sixty minute rest period. The hunger contractions are peristaltic in nature and start weakly in the region of the cardia or the lower part of the esophagus, sweep with augmenting strength over the entire stomach and gradually die out in the duodenum. In the normal person, the ordinary contractions produce intermittent distress or gnawing sensations, while the incomplete tetany which frequently terminates the period is definitely painful.

A satisfactory explanation is still wanting for the fact that hunger contractions initiate disagreeable sensations while digestive contractions do not. Digestive contractions were compared with hunger contractions by Rogers and Hardt[7] and Mulinos,[8] but no significant difference was

5. Hoelzel, F.: Central Factors in Hunger, Am. J. Physiol. **82**:665 (Nov.) 1927. Gulliksen, D. P.; Fogelberg, A., and Kardos, L.: Anorexia and Gastric Motility, Am. J. Digest. Dis. **5**:814 (Feb.) 1939. Wangensteen, O. H., and Carlson, H. A.: Hunger Sensations in a Patient After Total Gastrectomy, Proc. Soc. Exper. Biol. & Med. **28**:545 (Feb.) 1931.

6. Richter, C. P.: Animal Behavior and Internal Drives, Quart. Rev. Biol. **2**:307, 1937.

7. Rogers, F. T., and Hardt, L. L. J.: Contributions to the Physiology of the Stomach: XXVI. The Relation Between the Digestion Contractions of the Filled, and the Hunger Contractions of the "Empty" Stomach, Am. J. Physiol. **38**:274 (Aug.) 1915.

8. Mulinos, M. G.: The Gastric Hunger Mechanism: The Effect of Food upon the Empty Stomach and Its Relation to Hunger, Am. J. Physiol. **83**:115 (Dec.) 1927.

noted. Brody, Werle, Meschan and Quigley [9] studied the contractions by the fluoroscopic technic and simultaneously accurately determined the pressures in the pyloric antrum and the duodenal bulb by the optical registration method and found the motility similar during fasting and after feeding. However, in the latter state the basal pressures were increased, and the phasic pressure changes became more uniform.

Hunger contractions are inhibited most effectively by the ingestion of food and more transiently by the sight of food, by drinking water, by smoking, by psychic disturbances or by a variety of stimuli, especially those involving pain from any part of the body. The inhibition of hunger contractions by food does not result from food confined to the stomach. Distention of the stomach by any substance, such as a large balloon, fluid or gas, increases the frequency and magnitude of hunger contractions. However, the presence of food in the duodenum promptly and characteristically suppresses the motility. This inhibition is induced through the enterogastric reflex and through enterogastrone, which will be considered in greater detail in a later section of this paper.

The mechanism controlling the spontaneous initiation and termination of hunger contractions is unknown. Vagotomy tends to depress and splanchnicotomy to augment this motility in a characteristic manner. Nevertheless, hunger contractions occurring in the completely denervated stomach are strikingly similar in the transplanted gastric pouch and the main stomach from which it was made.[10] This indicates the action of an unidentified humoral factor. Tschukitscheff [11] presented evidence that transfusion of blood produced or inhibited hunger contractions in the recipient animal, depending on whether the blood was taken while the donor was showing active hunger contractions or was in a period of gastric rest. The active factor apparently is not the blood sugar level [12] or the amino acid concentration of the blood.[13]

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9. Brody, D. A.; Werle, J. M.; Meschan, I., and Quigley, J. P.: Interlumen Pressures of the Digestive Tract, Especially the Pyloric Portion, Am. J. Physiol. **130**:791 (Oct.) 1940.

10. Quigley, J. P.; Zettelman, H. J., and Ivy, A. C.: Analysis of the Factors Involved in Gastric Motor Inhibition by Fats, Am. J. Physiol. **108**:643 (June) 1934.

11. Tschukitscheff, J. P.: Ueber den Mechanismus der Hungerbewegungen des Magens: I. Einfluss des "satten" und "Hunger"—Blutes auf die periodische Tätigheit des Magens, Arch. f. d. ges. Physiol. **223**:251, 1930.

12. Quigley, J. P., and Halloran, W. R.: The Independence of Spontaneous Gastrointestinal Motility and Blood Sugar Levels, Am. J. Physiol. **100**:102 (March) 1932. Scott, W. W.; Scott, C. C., and Luckhardt, A. B.: Observations on the Blood Sugar Level Before, During and After Hunger Periods in Humans, ibid. **123**: 243 (July) 1938.

13. Bowman, H.; Regan, J. F., and Still, E. U.: The Effect of Intravenous Injections of Amino Acids on the Motility of the Stomach in Normal and Fasting Dogs, Am. J. Physiol. **112**:438 (July) 1935.

The evidence is convincing that hunger contractions through mechanical trauma to the area involved may give rise to considerable distress in the patient with ulcer and may also prevent healing of the ulcer. Hunger contractions should therefore be controlled. It is desirable but not practical to produce complete motor rest of the stomach in the patient with ulcer. The next best procedure, fortunately, is usually rather satisfactory and is extensively employed clinically. This consists of suppression of hunger contractions and a change of motility to the digestive type by frequent feedings.[14] It is especially desirable to avoid or relieve the conditions which tend to exaggerate hunger contractions (fasting or augmentation of the metabolic rate by hard physical labor, hyperthyroidism, exposure to cold, insulin hypoglycemia or diabetes).

Increase in gastric peristalsis and shortening of evacuation time roughly in proportion to the degree of hunger were noted by Ivy and Fauley.[15] Avoidance of this hypermotility with its attendant trauma to the sphincter region is one of the advantages of frequent feeding. Mann and Bollman observed that frequent feeding, especially of protein, may be beneficial in another way, for if dogs are fed, the capacity of the stomach to neutralize acid is exaggerated, even though the residues of food are flushed from the stomach.

Many patients with ulcer are well aware of the symptomatic relief which can be obtained by the ingestion of food and customarily take ful advantage of this subterfuge. This results in the ingestion of food, not primarily to balance unsatisfied metabolic needs but strictly to relieve somatic discomfort. In a patient with such a condition, hunger contractions have again become dominant in determining the intake of food—a superficial approximation of the primitive or infantile state. Owing to inaccuracies in the precise appreciation of ulcer pains, the food may be ingested even on occasions when the pain is not of the type amenable to food.

According to Norpoth,[16] Henning,[17] Scholtz and Brugsch,[18] Mensing and Kelly [19] and Hillman,[20] jejunal feeding produces motor and secretory

14. Sippy, B. W.: Gastric and Duodenal Ulcer: Medical Cure by an Efficient Removal of Gastric Juice, J. A. M. A. **64**:1625 (May 15) 1915. Meulengracht, E.: Treatment of Hematemesis and Melaena with Food, Acta med. Scandinav., 1934, supp. 59, p. 375. Treatment of Hematemesis and Melaena with Food: Mortality, Lancet **2**:1220 (Nov. 30) 1935.

15. Ivy, A. C., and Fauley, G. B.: The Effect of Hunger on the Emptying Time of the Stomach, Am. J. Physiol. **91**:206 (Dec.) 1929.

16. Norpoth, L.: Ueber jejunale Steuerung des Magenmotiliätat, Deutsches Arch. f. klin. Med. **176**:52, 1933.

17. Henning, N., and Norpoth, L.: Untersuchungen über die sekretorische Function des Magens während des nächtlichen Schlafes, Arch. f. Verdauungskr. **42**:12, 1928.

18. Scholtz, H. G., and Brugsch, J.: Untersuchungen bei der Jejunalsondenbehandlung des Ulcus ventriculi, Deutsches Arch. f. klin. Med. **175**:202, 1933.

(Footnotes continued on next page)

rest of the stomach, relieves the ulcer distress and promotes healing. However, these claims were not substantiated by Zukschwerdt and Eck.[21] At least a portion of the gastric inhibition produced by jejunal feeding results from intestinal distention. Schnedorf and Ivy[22] observed a decrease in hunger contractions or a delay in gastric evacuation from excessive smoking, but they were unable to explain why smoking usually exacerbates the ulcer condition.

ULCER PAIN

The pain fibers of the gastrointestinal tract ordinarily are insensitive to chemical or moderate mechanical stimuli. Hurst[23] considered that tension of the wall of the intestine constitutes the only adequate stimulus, and this concept is widely accepted but by no means proved. Good evidence has shown that either mechanical or chemical factors can induce ulcer distress, and it is possible that they produce their effect by augmenting the tension of the wall of the intestine. The pain experienced during fasting might result from hunger contractions or from acid in contact with the ulcer, and the ingestion of food may afford relief either by terminating the contractions or by adsorbing, neutralizing and diluting the gastric acid. The gnawing, intermittent type of ulcer pain is generally ascribed to hunger contractions; the continuous burning sensation may arise either from a spasm in the region of the ulcer, from the swelling and inflammation around the border of the ulcer or from contact of the ulcer with gastric acid. Since the hydrochloric acid–pepsin mixture exerts an anesthetic action on the human skin and does not produce pain in the normal stomach, it is suggested that in the patient with ulcer, gastric acid must act indirectly and produce pain by inducing abnormal motility in the vicinity of the ulcer.

Ulcer pain has been definitely correlated with hunger contractions.[24] Most investigators have found the hunger contractions of patients with

19. Mensing, E. H., and Kelly, E. H.: Total Suppression of Acid Gastric Secretion and Hunger Contractions by Means of Jejunostomy: Experimental and Clinical Study, Am. J. Surg. **20**:99 (April) 1933.

20. Hillman, O. S.: Jejunostomy in Treatment of Massive Gastric Ulcer, Brit. M. J. **1**:221 (Feb. 11) 1933.

21. Zukschwerdt, L., and Eck, T.: Die operative Behandlung des nichtresezierbaren peptischen Geschwüres, Deutsche Ztschr. f. Chir. **237**:457, 1932.

22. Schnedorf, J. G., and Ivy, A. C.: Effect of Tobacco Smoking on Alimentary Tract: Experimental Study of Man and Animals, J. A. M. A. **112**:898 (March 11) 1939.

23. Hurst, A. F.: The Sensibility of the Alimentary Canal, London, Oxford University Press, 1911.

24. Carlson, A. J.: Contributions to the Physiology of the Stomach: XLIV. The Origin of the Epigastric Pains in Cases of Gastric and Duodenal Ulcer, Am. J. Physiol. **45**:80 (Dec.) 1917. Ginsburg, H.; Tumpowski, I., and Hamburg, W. W.:

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ulcer normal or only slightly exaggerated, but Onodera [25] described an augmented type of motility which he considered typical of this disorder. The development of ulcer pains from normal hunger contractions is ascribed to concomitant hyperexcitability of the sensory mechanism in the gastrointestinal wall. This hypersensitivity may result from gastritis, the swelling and inflammation surrounding the ulcer, the action of hydrochloric acid [26] or similar factors.

In general, these conclusions are in accord with the significant observations of Dragstedt and Palmer [27] of a patient with an ulcer exposed under local anesthesia. Gentle rubbing of the ulcer with the finger produced severe and typical distress and severe pain resulted from compression or massage of the ulcer or traction on the duodenum. The introduction of sodium bicarbonate into the stomach relieved the distress, even though the traction was continued. The application of hydrochloric acid to the ulcer returned the distress, and this was again relieved by bicarbonate of soda. Later, a deep circular contraction ring developed just distal to the ulcer and was succeeded by several similar spasms, and all during this interval severe, cramplike pain persisted.

Clinicians frequently report the development of pyloric achalasia, spasm or stenosis from ulcer in close proximity to the sphincter. If such a condition exists, the hunger contractions are probably exaggerated and gastric evacuation retarded,[28] and a mechanism is available for augmentation of the ulcer distress.[29]

Contributions to the Physiology of the Stomach: XXV. The Newer Interpretation of the Gastric Pain in Chronic Ulcer, J. A. M. A. **67**:999 (Sept. 30) 1916. Dundon, J. R.: Contributions to the Physiology of the Stomach: XLIII. The Influence of Experimental Ulcers of the Stomach and Duodenum on the Hunger Contractions of the Empty Stomach, Am. J. Physiol. **44**:234 (Sept.) 1917. Christensen, O.: Pathophysiology of Hunger Pains, Acta med. Scandinav., 1931, supp. 37, p. 1. Dimitriu, C. C.; Tanasoca, T., and Popovici, A.: La douleur gastrique, étudiée par la méthode viscérographique, Presse méd. **46**:610 (April 20) 1938.

25. Onodera, N.; Kanegae, S.; Matufuzi, M., and Hasi, T.: Ueber die gastrographische Methode der Diagnose von Magenkrebs, Magen-Darm-Geschwür und Cholecystitis, Ztschr. f. klin. Med. **118**:354, 1931.

26. Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcer: I. Achlorhydria; II. The Production of Pain by Means of Chemical Irritants; III. The Role of Peristalsis and Spasm, Arch. Int. Med. **39**:109 (Jan.) 1927.

27. Dragstedt, L. R., and Palmer, W. L.: Direct Observations on the Mechanism of Pain in Duodenal Ulcer, Proc. Soc. Exper. Biol. & Med. **29**:753 (March) 1932.

28. (*a*) Elsesser, O. J.: Contributions to the Physiology of the Stomach: XXXI. The Effect of Experimental Partial Stenosis of the Pylorus on the Motility of the Empty Stomach, Am. J. Physiol. **39**:303 (Jan.) 1916. (*b*) Carlson, A. J., and Ginsburg, H.: Contributions to the Physiology of the Stomach: XXX. The Tonus and Contractions of the Empty Stomach of Infants with Congenital Pyloric

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THE STOMACH DURING DIGESTION AND EVACUATION

The motor activities of the stomach during digestion, consisting of the reception of a meal, the maceration, the fragmentation and the mixing of the food with the gastric juice and the discharge of the chyme into the duodenum may be detailed as follows: As food passes from the esophagus into the empty stomach, the walls which were in apposition are separated, and the stomach fills with a moderate increase in basal intragastric pressure.[30] The property of the stomach which enables it to function as a reservoir (to fill without a significant increase in pressure) has been ascribed, especially by Cannon, to "receptive relaxation," a loss of tone of the gastric wall initiated by a reflex from the esophagus. An inhibitory reflex is definitely involved, for a fall of intragastric pressure follows the smelling of food, and the intragastric pressures are transiently lower when the meal is given orally than those obtained by feeding through gastrostomy.[9] However, reflex inhibition is not the only factor involved, for considerable filling without significant increase of intragastric pressure may occur solely because of the physical relations involved.[31]

Much evidence indicates that food (especially fluids) passes preferentially along the gastric pathway (*Magenstrasse*). The inference that this scraping of food against the mucosa involves some trauma to the mucosa has been suggested as an explanation for the presence in this region of approximately 90 per cent of gastric ulcers,[32] but the idea has not been universally supported by the more recent roentgen studies.

The food in the stomach is held chiefly in the "hopper" (body and fundus). Here it undergoes but little mixing, so that the portions tend to persist for some time as discrete layers, arranged concentrically as ingested. This material is gradually liquefied; the fats melt, the proteins are attacked by pepsin and hydrochloric acid, and the starch is partially digested by ptyalin. The entire mass is subjected to moderate pressure due to the persistent tone in this region and to infrequent feeble peristaltic waves. Periodically, a portion of the mass is forced into the "mill"

Stenosis, Pylorospasm and Chronic Vomiting (Merycism), ibid. **39**:310 (Jan.) 1916. (*c*) Ivy, A. C.: Contributions to the Physiology of the Stomach: LII. Studies on Gastric Ulcer, Arch. Int. Med. **25**:6 (Jan.) 1920.

29. Wolfer, J. A.: Chronic Ulcer of the Stomach: Its Experimental Production and Effect on Gastric Secretion and Motility, Ann. Surg. **81**:89 (Jan.) 1925.

30. (*a*) Gianturco, C.: Some Mechanical Factors of Gastric Physiology: Empty Stomach and Its Various Ways of Filling; Pressure Exerted by Gastric Walls on Gastric Content; Physical Changes Occurring to Foodstuffs During Digestion, Am. J. Roentgenol. **31**:735 (June) 1934. (*b*) Brody and others.[9]

31. Grey, E. G.: Observations on the Postural Activity of the Stomach, Am. J. Physiol. **45**:272 (Feb.) 1918.

32. Aschoff, L.: Lectures in Pathology, New York, Paul B. Hoeber, 1924, p. 365.

(pyloric antrum) where it is mixed and broken up into fragments by powerful peristaltic waves which pass toward the sphincter. The contractions starting near the incisura require approximately thirty seconds to reach the pylorus. Those starting near the cardia require one to three minutes to reach the pylorus. From one to four waves can be seen on the stomach at one time during gastric evacuation.

Fluids usually begin to leave the stomach promptly (between one and four minutes after ingestion), but more solid material makes its first appearance in the duodenum after a longer period. The factors governing this early evacuation are not definitely known, but in general, materials which might be irritating to the duodenum are retained and modified to make them more acceptable. According to recent observations made in this laboratory, the normal course of events proceeds according to the following pattern: A small portion of gastric contents enters the intestine. If the sample proves satisfactory, the remainder leaves the stomach rapidly; unsuitable material initiates reactions from the duodenum which temporarily retard further gastric evacuation.

The rate of gastric evacuation is largely determined by the antral tonus, the antral contraction waves, the activity of the pyloric sphincter and the character of the food. The belief that gastric emptying is dominated chiefly by a stopcock action of the pyloric sphincter has been presented so thoroughly elsewhere [33] that it will not be repeated here. However, it should be emphasized that this concept was based largely on indirect evidence. Theoretic considerations and more direct observations by Thomas [34] of the factors involved tended to place antral activity as the chief factor in normal evacuation. In trained dogs, Meschan and Quigley [35] observed the rhythmic passage of peristaltic waves in a comparatively uniform cycle over the antrum, the sphincter and the duodenal bulb. These three portions of the alimentary canal were found to respond almost invariably in a similar manner to factors which changed their tone and motility.

Subsequent studies by Werle, Brody, Ligon, Read and Quigley [36] confirmed these observations and showed that evacuation occurred when a propulsive peristaltic contraction wave involved the distal part of the

33. Murlin, J. R.: The Emptying Mechanism of the Stomach, J. Nutrition **2**: 311 (Jan.) 1930. Alvarez, W. C.: An Introduction to Gastro-Enterology, New York, Paul B. Hoeber, Inc., 1940.

34. Thomas, J. E.: Some Physical and Physiological Factors Involved in the Regulation of Gastric Emptying, Rev. Gastroenterol. **2**:32 (March) 1935.

35. Meschan, I., and Quigley, J. P.: Spontaneous Motility of the Pyloric Sphincter and Adjacent Regions of the Gut in the Unanesthetized Dog, Am. J. Physiol. **121**:350 (Feb.) 1938.

36. Werle, J. M.; Brody, D. A.; Ligon, E. W., Jr.; Read, M. R., and Quigley, J. P.: The Mechanics of Gastric Evacuation, Am. J. Physiol. **131**:606 (Jan.) 1941.

antrum and a positive pressure gradient obtained from the antrum to the duodenal bulb. Direct methods of observation indicated that the sphincter probably did not exercise the dominant control of evacuation, especially since it was in a position which could retard evacuation for only one third to one fourth of each cycle. Further, the sequential relation of the sphincter contractions to the antral and bulbar contractions actually indicates that the sphincter is much more effective in preventing duodenal regurgitation than in blocking gastric evacuation.

These recent studies indicate that gastric evacuation is determined chiefly by the action of the antral pump, i. e., the antral and bulbar pressure gradient, the degree of antral tone and the depth of antral peristalsis and whether the waves persist or tend to die out as they approach the sphincter. When the antral wave travels to the sphincter and completely occludes the lumen as it progresses, practically all material distal to the antral peristaltic wave is expelled; but when these conditions do not obtain, the major portion returns to the body of the stomach. The situation is further modified by the fact that the portion expelled is chiefly the thinner material; larger lumps are retained for further fragmentation. During most of the evacuation period, the peristaltic waves begin in the region of the incisura angularis, but as the period nears its termination, the waves originate higher in the gastric body and are effective in the expulsion of the last portion of chyme.

Stretching of the gastric wall by a large balloon or by the ingestion of food exaggerates the evacuating motility of the sphincter region,[37] and the studies of Van Liere [38] showed that the evacuation rate of a large meal is greater than that of a smaller meal. Significant distention of the stomach, such as that which follows the ingestion of large meals, would be contraindicated in patients with ulcer since the augmented evacuation drive would involve greater trauma to the region of the ulcer.

As the stomach discharges, however, influences are initiated from the proximal part of the intestine which tend to suppress gastric motility and check evacuation. The presence of an excessive quantity of an indifferent substance, such as Ringer's solution, in the duodenum or of small quantities of more specific substances, such as fats,[10] hydrochloric acid,[39] protein split products,[40] sugars [41] or hypertonic solutions,[42] causes

37. Quigley, J. P.; Werle, J. M.; Ligon, E. W., Jr.; Read, M. R.; Radzow, K. H., and Meschan, I.: The Influence of Fats on the Motor Activity of the Pyloric Sphincter Region and on the Process of Gastric Evacuation Studied by the Balloon-Water Manometer and by the Optical Manometer-Fluoroscopic Technic, Am. J. Physiol. **134**:132 (Aug.) 1941.

38. Van Liere, E. J.; Sleeth, C. K., and Northup, D.: The Relation of the Size of the Meal to the Emptying Time of the Human Stomach, Am. J. Physiol. **119**:480 (July) 1937.

39. (*a*) Read, M. R.; Radzow, K. R.; Meschan, I.; Werle, J. M., and Quigley, J. P.: To be published. (*b*) Thomas, J. E.; Crider, J. O., and Mogan, C. J.:

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more or less complete inhibition of the entire region of the sphincter—the antrum, the sphincter and the bulb. The antrum is the most profoundly inhibited structure of these three. (A transient period of augmented activity of the bulb and the sphincter may occur while the material is being expelled from the bulb.) Inhibition of the region of the sphincter results from a reflex (the enterogastric reflex) and the action of an inhibitory hormone (enterogastrone) originating in the duodenum. Thus, the presence of significant quantities of these substances in the chyme discharged into the duodenum suppresses the antral evacuating drive (propulsive peristalsis), delays evacuation and frequently decreases gastric secretion.[43]

This "autoregulation" of the rate and the character of the material evacuated deserves considerable emphasis, since through its operation much chemical and mechanical trauma to the region of the sphincter is avoided. No doubt the mechanism is significant in reducing the tendency of ulcers to form or in permitting them to heal. Advantage is taken of this principle to suppress gastric motor and secretory activity in the clinical management of ulcer by employing frequent feedings with especial emphasis on a diet high in fat. This is exemplified by the routine care of ulcer advocated by Sippy and in the early feeding after ulcer hemorrhage emphasized by Meullengracht. Depression of gastric motor and secretory activity by the administration of enterogastrone extracted from the intestinal mucosa has been successfully employed to prevent experimental gastrojejunal ulcer.[44] It is not definitely known how the presence of peptic ulcer modifies the autoregulation mechanism or the role which modifications of this mechanism may have in the production or maintenance of an ulcer, but these problems should be investigated.

A Study of Reflexes Involving the Pyloric Sphincter and Antrum and Their Role in Gastric Evacuation, Am. J. Physiol. **108**:683 (June) 1934.

40. Thomas, J. E., and Crider, J. O.: Inhibition of Gastric Motility Associated with the Presence of Products of Protein Hydrolysis in the Upper Small Intestine, Am. J. Physiol. **126**:28 (May) 1939.

41. Quigley, J. P., and Phelps, K. R.: The Mechanism of Gastric Motor Inhibition from Ingested Carbohydrates, Am. J. Physiol. **109**:133 (July) 1934.

42. Gershon-Cohen, J.; Shay, H., and Fels, S. S.: Experimental Studies on Gastric Physiology in Man: Influence of Osmotic Pressure Changes of Salt and Sugar Solutions on Pyloric Action and Gastric Emptying in Normal and Operated Stomach, Am. J. Roentgenol. **40**:335 (Sept.) 1938.

43. Kosaka, T., and Lim, R. K. S.: Demonstration of the Humoral Agent in Fat Inhibition of Gastric Secretion, Proc. Soc. Exper. Biol. & Med. **27**:890, 1930. Kosaka, T.; Lim, R. K. S.; Ling, S. M., and Liu, A. C.: On the Mechanism of the Inhibition of Gastric Secretion by Fat: A Gastric-Inhibitory Agent Obtained from the Intestinal Mucosa, Chinese J. Physiol. **6**:107 (Feb. 15) 1932.

44. Hands, A. P.; Fauley, G. B.; Greengard, H., and Ivy, A. C.: Prevention of Experimental Gastrojejunal Ulcer by Enterogastrone, Am. J. Physiol. **133**: P314 (June) 1941.

In an attempt to reduce trauma in the pyloric region, sectioning of the vagi has been suggested as a method of treating peptic ulcer [45] or vagotonia.[46] Knowledge of the effects of vagotomy on the gastric motor and secretory activity of animals is still rather incomplete, and with regard to man the situation is even less satisfactory. Therefore this procedure should be undertaken with caution. From what is known in this field, it may be stated that vagotomy may have the desirable effect of eliminating gastric secretion induced reflexly over the vagi but that the response to a test meal would remain normal.[47] Decreased motor drive would develop,[48] the initial evacuation of fluids might be hastened, but the time required for complete evacuation of solids would be delayed. Some stagnation of the gastric contents, especially particulate matter, might occur, and this would be undesirable since prolongation of the contact of food with gastric mucosa would exaggerate the gastric phase of gastric secretion, and gastric juice of high acid concentration would collect. Vagotomy does not modify the normal sequential relation of contraction waves over the antrum, the sphincter and the bulb or produce a significant relaxation of this region in the dog.[49] The more undesirable effects of vagotomy would involve a suppression of the enterogastric reflex [39b] and a modification of enterogastrone activity so that autoregulation of gastric activity from the intestine would be practically eliminated. Beazell and Ivy [50] observed that chronic gastric ulcer followed bilateral vagotomy in the rabbit and less frequently in the dog when these were fed a rough diet. Marked histologic and functional changes were noted after vagotomy by Lasowsky and Ptschelina,[51] while Best and Orator [52] considered vagotomy of little value in the treatment of peptic ulcer.

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45. Winkelstein, A., and Berg, A. A.: Vagotomy Plus Partial Gastrectomy for Duodenal Ulcer, Am. J. Digest. Dis. **5**:497 (Oct.) 1938. Mayo, C. H.: Division of the Vagi for Pylorospasm, Ann. Surg. **88**:669 (Oct.) 1928.

46. Barron, L. E., and Curtis, G. M.: Effect of Vagotomy on Gastric Motor Mechanism of Man, Arch. Surg. **34**:1132 (June) 1937.

47. Ferguson, J. H.: Effects of Vagotomy on Gastric Functions of Monkeys, Surg., Gynec. & Obst. **62**:689 (April) 1936.

48. Meek, W. J., and Herrin, R. C.: Effect of Vagotomy on Gastric Emptying Time, Am. J. Physiol. **109**:221 (Aug.) 1934.

49. Quigley, J. P., and Meschan, I.: The Role of the Vagus in the Regulation of the Pyloric Sphincter and Adjacent Portions of the Gut, with Especial Reference to the Process of Gastric Evacuation, Am. J. Physiol. **123**:166 (July) 1938.

50. Beazell, J. M., and Ivy, A. C.: Chronic Gastric Ulcer Following Bilateral Vagotomy in Rabbit and in Dog, Arch. Path. **22**:213 (Aug.) 1936.

51. Lasowsky, J. M., and Ptschelina, A. N.: Ueber trophische Magenstörungen unter der Einwirkung beiderseitiger Vagotomie, Experimentelle morphologische Untersuchung, Virchows Arch. f. path. Anat. **285**:755, 1932.

52. Best, R. R., and Orator, V.: Vagus Nerve and Its Relation to Peptic Ulcer, Ann. Surg. **96**:184 (Aug.) 1932.

STAGNATION OF GASTRIC CONTENTS

As gastric juice is normally secreted, it has an acidity of approximately 0.5 per cent.[53] This exceeds the acidity usually found for gastric contents (0.1 per cent hydrochloric acid or less), because under physiologic conditions gastric juice is neutralized and diluted: (1) by swallowed food, water and saliva; (2) by the secreted mucus, especially of the pyloric antrum, and (3) by regurgitated duodenal contents.

The studies of Boldyreff [54] and subsequent investigators showed that regurgitation of alkaline duodenal contents ordinarily occurs when the acidity of the gastric contents is excessive. This results in a dilution and neutralization of gastric acid with a consequent decrease in acidity to the normal range.

Dragstedt [55] and others presented evidence indicating that gastric contents approaching the composition of the pure secretion of the gastric glands (i. e., having a hydrochloric acid concentration in excess of 0.15 per cent) will digest the normal gastric wall. Thus it may be assumed that interference with either gastric evacuation or regurgitation can produce stagnation, hyperacidity and, finally, peptic ulcer. Hurst [56] observed an increase in volume and acidity of gastric juice in 60 per cent of a group of patients with ulcer, and in general the clinical data substantiates the view that gastric hyperacidity is commonly associated with ulcer, but it is frequently a debatable point whether the hyperacidity is the cause or the result of the ulcer.

Certain types of stagnation exaggerate and prolong gastric motility and gastric secretion; this favors production and maintenance of ulcer. Experimental stagnation of gastric contents was produced by folding the anterior wall of the stomach to produce an hourglass effect (Baggio). This resulted in lesions ranging from simple erosion to typical ulcer. Slocomb [57] made a partial obstruction of the duodenum of dogs and subsequently observed inflammatory changes and multiple ulcers. Fre-

53. Hollander, F.: The Composition of Pure Gastric Juice, Am. J. Digest. Dis. & Nutrition **1**:319 (July) 1934; Studies in Gastric Secretion: V. The Composition of Gastric Juice as a Function of Its Acidity, J. Biol. Chem. **104**: 33 (Jan.) 1934. Carlson.[2]

54. Boldyreff, W.: The Self-Regulation of the Acidity of the Gastric Contents and the Real Acidity of the Gastric Juice, Quart. J. Exper. Physiol. **8**:1, 1915.

55. Dragstedt, L. R.: Some Physiological Principles Involved in Surgical Treatment of Gastric and Duodenal Ulcer, Ann. Surg. **102**:563 (Oct.) 1935.

56. Hurst, A. F.: Scharstein Lecture on Precursors of Carcinoma of the Stomach, Lancet **2**:1023 (Nov. 16) 1929.

57. Slocomb, L. H.: Experimental Gastroduodenal Ulcer Produced by Partial Obstruction of the Duodenum, J. Missouri M. A. **24**:351 (Aug.) 1927.

quently, ulcer has been associated with the stagnation produced by a diaphragmatic hernia.[58]

Steinberg and Starr[59] prevented spasm in the first part of the jejunum of Mann-Williamson dogs when they stripped the muscularis from the jejunum at its anastomosis with the stomach. Ulcer was subsequently absent from the stripped region but readily formed at the first portion of the jejunum having an intact muscle. Fauley and Ivy[60] repeated the experiment with a modified technic. Although the previous studies were not invalidated, these investigators demonstrated that a local spasm in the jejunum was not essential to the production of ulcer near the anastomosis. Inhibition of gastric motility may result from emotional stress, and the resulting stagnation of strong gastric juice may be a factor in the causation of ulcers ascribed to nervousness, worry and other emotional states.[61]

Gastric retention resulting clinically from interference with normal gastric evacuation or regurgitation is generally considered as an important factor in the maintenance of ulcer. This stagnation has been ascribed to functional abnormalities of the sphincter—pylorospasm or absence of normal relaxation, achalasia—or to pyloric cicatrization.[62] Although spasms in the vicinity of an ulcer are common, they usually disappear under therapy, but cicatrization follows. Unless the spasm or scarring is extensive or involves adhesions which distort the viscus, they are usually not important from the motor standpoint.[63]

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58. Harrington, S. W.: Diaphragmatic Hernia Associated with Traumatic Gastric Erosion and Ulcer, Surg., Gynec. & Obst. **51**:504 (Oct.) 1930. Truesdale, P. E.: Gastric Ulcer Associated with Diaphragmatic Hernia, New England J. Med. **207**:385 (Sept. 1) 1932.

59. Steinberg, M. E., and Starr, P. H.: The Factor of Spasm in the Etiology of Peptic Ulcers, Arch. Surg. **29**:895 (Dec.) 1934.

60. Fauley, G. B., and Ivy, A. C.: The Factor of Spasm in the Etiology of Jejunal Ulcer, Am. J. Digest. Dis. & Nutrition **4**:160 (May) 1937.

61. Rivers, A. B.: Clinical Consideration of Etiology of Peptic Ulcer, Arch. Int. Med. **53**:100 (Jan.) 1934. Todd, T. W.: Behavior Patterns of the Alimentary Tract, Baltimore, Williams & Wilkins Company, 1930.

62. Lahey, F. H.: Treatment of Gastric and Duodenal Ulcer, J. A. M. A. **95**: 313 (Aug. 2) 1930. Ivy, A. C., and Fauley, G. B.: Factors Concerned in Determining Chronicity of Ulcers in Stomach and Upper Intestine: Susceptibility of Jejunum to Ulcer Formation; Effect of Diet on Healing of Acute Gastric Ulcer, Am. J. Surg. **11**:531 (March) 1931. Hurst, A. F.: Alvarez Lecture on Unity of Gastric Disorders, Brit. M. J. **2**:89 (July 15) 1933. Miller, R. H.: Present-Day Review of Gastric and Duodenal Ulcer, New England J. Med. **206**:925 (May 5) 1932. Hughson, W.: Reflex Spasm of the Pylorus and Its Relation to Diseases of the Digestive Organs, Arch. Surg. **11**:136 (July) 1925. Wolfer, J. A.: Chronic Experimental Ulcer of the Stomach: Its Clinical Significance, J. A. M. A. **87**:725 (Sept. 4) 1926. Ivy.[28c]

63. Jordan, S. M.: Review of Gastric Ulcer Problem, J. A. M. A. **107**:1451 (Oct. 31) 1936.

Various surgical procedures involving gastroenterostomy or pyloroplasty have been employed in the attempt to restore the physiologic relations by overcoming stagnation and also permitting the return of intestinal contents to the stomach. Frequently, these measures have failed to produce clinical relief. In many cases, this was related to the fact that interference with free communications between the stomach and the intestine did not obtain preoperatively. Clinical signs of pylorospasm or achalasia are based almost entirely on indirect observations and therefore are frequently misleading, but patients exhibiting definite functional or anatomic pyloric obstruction may anticipate improvement from suitable surgical intervention.

It is generally believed that the presence of hyperacidity produces pylorospasm and thus sets up a vicious circle. This theory may be questioned since it was based on indirect evidence which indicated that acid in the duodenum caused firm closure of the pyloric sphincter. Thomas, Crider and Mogan [39b] and Read, Ligon, Meschen and Quigley [39a] showed by direct methods that hydrochloric acid in the duodenum of the normal dog in concentrations similar to or even exceeding that of chyme does not produce pylorospasm. In fact, the predominant effect is inhibition of the entire region of the sphincter. When injected into the duodenal bulb, hydrochloric acid moderately increases rhythmic contractions of the sphincter for a brief interval, but this is followed by a relaxation of the entire region of the sphincter. Ulcer in close proximity to the sphincter is generally believed to produce pylorospasm, but since this theory also is based on indirect evidence, it should be accepted with reserve until substantiated by more direct evidence.

MECHANICAL TRAUMA

Trauma to the digestive tract is not essential to the formation of ulcer. However, in many cases trauma appears to be a contributing factor or occasionally even the major factor in the development and maintenance of ulcer. This is emphasized by the fact that the marked pressure changes associated with vomiting may readily produce gastric hemorrhage or ulceration. It was previously mentioned that trauma resulting from the scraping of material along the gastric pathway (*Magenstrasse*) tends to explain the high incidence of ulcer in that region. It is significant also that experimental lesions produced in this region heal more slowly than those along the greater curvature. Mann and Bollman [64] observed that experimental ulcers produced by toxic factors are almost always in the pathway of the outflow of gastric contents.

64. Mann, F. C., and Bollman, J. L.: Experimentally Produced Peptic Ulcers: Development and Treatment, J. A. M. A. **99**:1567 (Nov. 5) 1932. Mann, F. C.: Mechanism of Peptic Ulceration: Review of Results of Experimental Investigation, Brit. M. J. **1**:707 (April 8) 1939.

Also related to this trend of thought is the fact that a diet of coarse food increases the incidence of ulcer in an Eck fistula or in bilaterally vagotomized animals. Fauley and Ivy [65] delayed the healing of experimental ulcers by feeding food containing much roughage. Ulcers were produced in prematurely weaned calves by Konjetzney and Puhl [66] by feeding rough food. The calves, however, were poorly nourished, and this fact introduced an additional factor into the investigation but did not invalidate the experiments.

It has been observed both clinically and experimentally that when gastric contents are expelled in such a manner that they strike a region with some force, an ulcer may be induced or, if already present, may fail to heal. In dogs prepared by the Mann-Williamson [67] technic and observed by Mann and Bollman,[64] the site of the formation of ulcer is typical, constant and within limits can be modified. Normally, the ulcer forms 1 to 2 cm. distal to the point of exit of the gastric contents and in the area where the material strikes first and with the greatest force. After the ulcer is formed, if the jejunal segment leaving the stomach is made to continue in the same direction as the pylorus for several inches and then bend sharply, the first ulcer, relieved from the major mechanical trauma (although exposed to the same chemical environment), heals, while a second ulcer will form at the intestinal bend. Restriction of the opening between the stomach and the intestine to produce a nozzle effect causes the ulcer to develop and perforate more rapidly. On the contrary, if the propulsive force of the stomach is decreased by surgically producing an hourglass defect in the prepyloric region, the rate of the formation of ulcer is decreased. Morton [68] produced duodenitis (probably a precursor to the formation of ulcer) by encircling the pylorus with a constricting band of jejunal muscle.

A significant contribution by Mann and Bollman to the ulcer problem does much to explain and correlate the observations just mentioned and others of a similar nature. The first step in the process of ulcer healing, according to them, consists of the formation of a delicate membrane over the ulcer. This film is readily removed by a variety of mechanical or chemical factors, and the healing process then remains practically in abeyance during the gradual process of forming a new membrane.

The fact that mechanical trauma to the mucosa is significant in the genesis and the maintenance of peptic ulcer is further supported by a

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65. Fauley, G. B., and Ivy, A. C.: Experimental Gastric Ulcer: Effect of Consistency of Diet on Healing, Arch. Int. Med. **46**:524 (Sept.) 1930.

66. Konjetzney, G. E., and Puhl, H.: Das sogenannte Ulcus pepticum des Magens der Absatzkälber, Virchows Arch. f. path. Anat. **262**:615, 1926.

67. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409 (April) 1923.

68. Morton, C. B.: Peptic Ulcer: Chronic Lesions of Duodenum Following Experimentally Produced Pyloric Dysfunction, Arch. Surg. **28**:467 (March) 1934.

variety of observations. The trauma incident to the presence of foreign bodies in the stomach was reported by Wheeler,[69] Eusterman and Mayo,[70] Schulze,[71] Balfour and Good [72] as a cause of chronic ulceration. Further, a portion of the success attendant on the use in ulcer therapy of bland or mucilaginous substances (mucin [73] and okrin [74]) is related to their capacity to decrease trauma in the area of the ulcer. Fauley and Ivy [75] considered the prevention of postoperative jejunal ulcer by the use of bland diets and fundusectomy.

The impression is current that successful therapy of ulcer involves reducing the motor drive of the stomach, keeping the pyloric sphincter patent and promoting gastric evacuation. Pituitary extract reduces the tone and the motility of the stomach,[76] and this action may contribute to the favorable results claimed for this substance in the treatment of ulcer.[77] Alkalis, such as sodium bicarbonate, have enjoyed extensive employment in ulcer therapy, partially because these substances hasten gastric evacuation.[78] However, according to Meschan and Quigley,[79] this augmented evacuation is not without serious clinical objections since it results from an increased gastric motor drive and occurs in spite of increased activity of the pyloric sphincter.

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69. Wheeler, P. H.: Enormous Benign Gastric Ulceration Caused by Multiple Foreign Bodies, New England J. Med. **214**:830 (April 23) 1936.

70. Eusterman, G. B., and Mayo, J. G.: Traumatic Peptic Ulcer, Am. J. Surg. **26**:74 (Oct.) 1934.

71. Schulze, V. E.: Persimmon Bezoar, with Report of a Case, South. M. J. **25**:833 (Aug.) 1932.

72. Balfour, D. C., and Good, R. V.: Phytobezoar Associated with Gastric Ulcer: Especial Reference to Persimmon Bezoar with Report of a Case, Am. J. Surg. **6**:579 (May) 1929.

73. Fogelson, S. J.: Treatment of Peptic Ulcer with Gastric Mucin: Preliminary Report, J. A. M. A. **96**:673 (Feb. 28) 1931; Gastric Mucin Treatment for Peptic Ulcer: Report on Questionnaires, Arch. Int. Med. **55**:7 (Jan.) 1935.

74. Jones, K. K.; Ivy, A. C., and Atkinson, A. J.: Treatment of Peptic Ulcer with Okrin: Preliminary Report, Illinois M. J. **63**:377 (April) 1933. Meyer, J.; Sidmon, E. E., and Necheles, H.: Treatment of Peptic Ulcer with Powdered Okra, Illinois M. J. **64**:339 (Oct.) 1933.

75. Fauley, G. B., and Ivy, A. C.: Prevention of Postoperative Jejunal Ulcers by Diet and Fundusectomy: Experimental Study in Dogs, Surg., Gynec. & Obst. **63**:717 (Dec.) 1936.

76. Quigley, J. P., and Barnes, B. O.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: VI. Antagonistic Action of Posterior Pituitary Lobe Preparations, Am. J. Physiol. **95**:7 (Oct.) 1930.

77. Metz, M. H., and Lackey, R. W.: Peptic Ulcer Treated by Posterior Pituitary Extract, Dallas M. J. **24**:46 (April) 1938; Gastric Lesion Produced by Posterior Pituitary Extract, Texas State M. J. **34**:214 (Aug.) 1938.

78. Van Liere, E. J., and Sleeth, C. K.: The Emptying Time of the Normal Human Stomach as Influenced by Acid and Alkali, with a Review of the Literature, Am. J. Digest. Dis. **7**:118 (March) 1940.

79. Meschan, I., and Quigley, J. P.: To be published.

PERFORATION OF ULCER

As the depth of the erosion of peptic ulcer increases, the ease of perforation usually increases. Generally, the actual perforation results from an intragastric pressure greater than the intra-abdominal pressure, and this pressure gradient is always essential to the escape of gastric contents into the peritoneal cavity. Until accurate determinations have been made simultaneously within and outside the gastrointestinal wall under a variety of conditions, many important details regarding the mechanism of perforation must remain obscure. However, the essential pressure gradient and the resulting perforation apparently may develop from the weight of a column of gastric contents, loading the stomach with a large meal, vigorous gastric or duodenal contractions, manipulation or nonpenetrating trauma to the abdomen.[80] Hemorrhage from an ulcer or perforation of an ulcer apparently is rarely the direct result of physical exertion.[81] Straining and similar exertion produces a general increase of intra-abdominal pressure, but this apparently cannot directly cause rupture. In respect to the effects of physical exertion on the pressures developed by the stomach itself, it has been found that vigorous exercise produces an early decrease in gastric motility, but increased gastric motility usually is a delayed effect of hard work and an early effect of mild exercise.[82]

OPERATION IN THE REGION OF THE PYLORIC SPHINCTER

Surgical treatment of an ulcer is usually avoided except in cases of severe pyloric obstruction, intractable hemorrhage, perforation or ulcer repeatedly demonstrated not to be ameliorated by the standard medical management. When recourse to operation appears warranted, procedures

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80. Corlette, C. E.: Trauma in Relation to Organic Visceral Disease, M. J. Australia **2**:587 (Nov. 7) 1931. Paas, H. R.: Ueber die Magen- und Duodenalperforation nach Röntgen-Kontrastmahlzeit und ihre Folgen, Deutsche Ztschr. f. Chir. **247**:461, 1936.

81. Meyer, K. A., and Brams, W. A.: Acute Perforation of Gastric and Duodenal Ulcer, Am. J. M. Sc. **171**:510 (April) 1926. White, F. W.: The Etiology and Pathology of Perforating Gastric and Duodenal Ulcers, Boston M. & S. J. **177**:555 (Oct. 18) 1917. Rhodes, G. K., and Collins, D. C.: Acute Perforated Peptic Ulcers: A Clinical Review of One Hundred and Fifty-Five Consecutive Patients Treated Surgically, California & West. Med. **39**:173 (Sept.) 1933. Beams, A. J.: Some Industrial Aspects of Acute Perforation and Hemorrhage of Peptic Ulcer, Ohio State M. J. **32**:130 (Feb.) 1936. Workmen's Compensation Acts: Perforation of Peptic Ulcer Allegedly Due to Strain, Bureau of Legal Medicine and Legislation; Medicolegal Abstracts, J. A. M. A. **106**:411 (Feb. 1) 1936.

82. Hellebrandt, F. A., and Tupper, R. H.: Studies on the Influence of Exercise on the Digestive Work of the Stomach: II. Its Effect on Emptying Time, Am. J. Physiol. **107**:355 (Feb.) 1934.

intended to eliminate the functional activity of the pyloric sphincter are commonly employed. Such operations are undoubtedly of value in many cases in that they remove serious interference with duodenal regurgitation [83] or hasten gastric evacuation and thus reduce the acidity and the volume of the gastric contents. These possible modifications do not always explain the beneficial effects of operation on ulcer, for relief is frequently obtained when the operative procedure is not followed by alteration in the gastric acidity or the evacuation rate.

In the presence of gross mechanical obstruction of the pylorus, operations designed to eliminate the functional activity of the sphincter can be depended on to shorten the gastric evacuation time. However, the time for complete evacuation generally returns only to the normal and most observers agree that gastric dumping is not the usual effect of such operations. Evacuation still requires a pressure gradient from the stomach to the intestine, and this probably cannot be supplied by gravity or respiratory movements as has been suggested. It is dependent on gastric peristaltic waves which develop pressure in the stomach adequate to expel its contents and also on intestinal waves which propel material along the intestine and prevent the development of excessive intestinal back pressure. Thus it has been demonstrated that if the pylorus is patent, even though partially obstructed, much of the gastric contents and especially the more solid material is discharged through the pylorus rather than through any artificial opening.[84] This is understandable, since a more effective expulsion pressure gradient can be developed at the sphincter than at any other portion of the stomach. Much of the material evacuated through the pyloric sphincter reenters the stomach through a gastroenterostomy stoma. Since this material reduces gastric acidity, the return of a moderate volume is desirable; but if the intestinal loop draining the stoma is obstructed, the gastric contents may travel in a vicious circle. This was noted especially by the pioneers with this operation.

After pyloroplasty in the cat, the early stage of gastric evacuation is more rapid than normal.[85] However, most investigators have found the time for complete evacuation essentially normal, and the various food substances known to retard evacuation (e. g., fats, hypertonic salt or sugar solutions) still exercise their characteristic delaying effect.

83. Deaver, J. B., and Burden, V. G.: Further Experience with Resection of Anterior Half of Pyloric Sphincter, Ann. Surg. **92**:533 (Oct.) 1930.

84. (*a*) Kelling, G.: Studien zur Chirurgie des Magens, Arch. f. klin. Chir. **62**:1, 1900. (*b*) Cannon, W. B., and Blake, J. B.: Gastro-Enterostomy and Pyloroplasty: An Experimental Study by Means of the Roentgen Rays, Ann. Surg. **41**:686, 1905.

85. Pannett, C. A.: An Experimental Investigation of the Results of Linear Division of the Pyloric Sphincter, Brit. J. Surg. **8**:262 (Jan.) 1921. Cannon and Blake.[84b]

This has been demonstrated in the dog following pylorosection [86] after mechanically propping the sphincter open,[87] after sectioning the pyloric sphincter or producing a gastroenterostomy [88] and after Billroth I or Polya resections or gastroenterostomy.[89] Similar results have been demonstrated in human subjects by Case,[90] Gaither,[91] Kirschner,[92] Beresow and Stern.[93] Shay and Gershon-Cohen [94] reported moderate shortening of the evacuation time of barium sulfate and water in the human being after Billroth I or Polya resections, and food substances produced slightly less retardation than in patients on whom operation was not performed. Such a deviation from normal can be chiefly ascribed to the fact that the test substances were introduced into a lower section of the intestine, since it has repeatedly been demonstrated that the antral inhibition produced by the enterogastric reflex or by enterogastrone is

86. von Mering, J.: Ueber die Funktion des Magens, Verhandl. d. deutsch. Cong. f. inn. Med. **15**:433, 1897. Thompson, H. L.: Resection of Pylorus—Its Effect on Secretory and Motor Functions of Stomach, California & West. Med. **36**:383 (June) 1932. Medoff, J.; Neuwelt, F.; Patedjl, J., and Necheles, H.: A Study of the Functions of the Stomach Following Pyloric Obstruction and Gastrostomy, Am. J. Physiol. **133**:386 (June) 1941.

87. Crider, J. O., and Thomas, J. E.: A Study of Gastric Emptying with the Pylorus Open, Am. J. Digest. Dis. & Nutrition **4**:295 (July) 1937.

88. Crisler, G. R., and Van Liere, E. J.: Pyloroplasty, Gastroenterostomy, and Partial Parasympathetic Denervation of the Pyloric Sphincter, and Their Relation to the Emptying Time of the Stomach, Am. J. Digest. Dis. & Nutrition **3**:167 (May) 1936. Gianturco.[30a]

89. Johnston, C. G., and Ravdin, I. S.: Action of Glucose on Emptying of Stomach: Effect of Varying Concentrations in Both Normal Stomachs and After Various Gastric Operations, Ann. Surg. **101**:500 (Jan.) 1935. Ravdin, I. S.; Pendergrass, E. P.; Johnson, C. G., and Hodes, P. J.: Effect of Foodstuffs on Emptying Normal and Operated Stomach and Small Intestinal Pattern, Am. J. Roentgenol. **35**:306 (March) 1936. Tanaka, K.: Observations and Kinematographic Studies Through Korwaischen Fistulae of the Movements of Operated Stomachs and Intestines in Dogs and Cats, Ztschr. d. jap. Chir. Gesellsch. **36**:122, 1935.

90. Case, J. T.: Gastric and Duodenal Roentgen-Ray Findings After Operation, J. A. M. A. **85**:1385 (Oct. 31) 1925.

91. Gaither, E. H.: Effects of Surgery of the Stomach on Its Subsequent Motor and Secretory Functions, J. A. M. A. **91**:1075 (Oct. 13) 1928.

92. Kirschner, M., and Mangold, E.: Die motorische Funktion des Sphincter Pylori und des Antrum beim Hunde nach der queren Durchtrennung des Magens, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:446, 1911; Centralbl. f. Chir. **56**:844, 1929.

93. Beresow, E., and Stern, N.: Die Arbeitsleistung des nach Billroth I operierten Magens, Deutsche Ztschr. f. Chir. **236**:465, 1932.

94. Shay, H., and Gershon-Cohen, J.: Experimental Studies in Gastric Physiology in Man: The Mechanism of Gastric Evacuation After Partial Gastrectomy as Demonstrated Roentgenologically, Am. J. Digest Dis. & Nutrition **2**:608 (Dec.) 1935.

elicited with much less intensity from portions of the intestine other than the proximal portion of the duodenum.

Schekhter [95] and others noted that evacuation is rhythmic after resection of the pylorus. This is due chiefly to the expulsion of material by rhythmic peristaltic waves of the stomach. The fact must also be considered that the sphincter function is not a unique property of the pylorus but is also possessed in some degree by antral muscle. This is indicated by the evidence presented by Meyer and Schmidt [96] that sphincter action may develop at any gastrointestinal anastomosis. From gastroscopic observations Schindler and Dailey [97] also concluded that the development of typical sphincter activity is a general property of any portion of the antrum. When observed by this technic, gastroenterostomy stomas usually remained gaping and motionless, but occasionally displayed sphincter action—rhythmically opening and closing in stellate fashion. The two sphincters did not uniformly act synchronously even when only a few centimeters apart. Cannon and Blake [84b] and Case [90] ascribed the rhythmic discharge of gastric contents and the essentially normal evacuation rate observed after sectioning the pyloric sphincter to rhythmic contractions of muscle rings in the duodenum. Thus it is evident that elimination of the functional activity of the pyloric sphincter may influence the process of gastric evacuation but slightly, either because the normal influence of the sphincter on emptying is only moderate or because adjacent structures develop a vicarious sphincter action.

Results not in accord with those presented have been reported by several authors. After subtotal gastric resection, Strauss and associates [98] found the emptying time, the character of the hunger contractions and the size of the stomach subject to considerable variation. Review of the literature and personal observations led Vitkin [99] to conclude that resection of the stomach produced considerable change in the form, the tone and the topographic relations of the stomach. The stomach became feeble and distended; food was insufficiently macerated, mixed or digested and was evacuated too rapidly. Carty, Weintraub

95. Schekhter, I. A.: Form, Localization and Motor Function of the Stomach After Resection for Ulcer, Novy Khir. Ark. (no. 163) **41**:346, 1938.

96. Meyer, H., and Schmidt, W.: Der operierte Magen, Ergebn. d. med. Strahlenforsch. **4**:479, 1930.

97. Schindler, R., and Dailey, M. E.: Gastroscopic Observations on Gastric Motility, Am. J. Digest. Dis. **8**:8 (Jan.) 1941.

98. Strauss, A. A.; Strauss, S.; Lewitsky, P.; Schenan, L.; Seidon, E. E.; Arens, R. A.; Meyer, J., and Necheles, H.: Physiological and Clinical Studies of Patients After Subtotal Gastrectomy, Am. J. Digest. Dis. & Nutrition **4**:32 (March) 1937.

99. Vitkin, S. F.: Motor Functions of the Stomach After Resection, Ann. Surg. **111**:27 (Jan.) 1940.

and Felter [100] claimed that after gastroenterostomy, gastric resection or pyloroplasty, only those patients responded well whose stomach was smaller, higher, more lateral than normal and displayed diminished peristalsis and rapid evacuation. They considered return of vigorous gastric peristalsis, increase in the size of the stomach and reestablishment of gastric discharge through the sphincter as indications of failure of the operative procedure. The differences in opinion in this field here outlined result in part from variations in the surgical technic employed, as well as in the method and the time of observation following the surgical intervention.

According to Truesdale,[101] Horwitz, Alvarez and Ascanio,[102] the presence of gastric and duodenal ulcer results in hypertrophy of the pylorus, especially the sphincter, and consequently pyloric obstruction develops. They also presented evidence which indicates that gastroenterostomy leads to atrophy of the pyloric musculature. The edema due to trauma incident to anastomosis of the stomach and the intestine by Billroth I or II resection persists for only a short time, but Mecray, Barden and Ravdin,[103] Barden, Ravdin and Frasier,[104] Hoelzel and Da Costa [105] showed that hypoproteinemia, which is frequently present in patients subjected to such operations, produces edema of the stomach and inhibition of gastrointestinal motility parallel to the degree of hypoproteinemia. This may cause sufficient edema of the stoma to retard gastric evacuation greatly until the deficiency of protein is relieved.

SUMMARY

The normal and abnormal motor activities of the stomach and the proximal portion of the intestine which characterize hunger, gastric evacuation, duodenal regurgitation, hypermotility or hypomotility, spasm and stagnation have important relations to the ulcer problem. Hunger contractions or spasms involving the ulcer region are among the chief

100. Carty, J. R.; Weintraub, S., and Felter, R. K.: An X-Ray Study of the Post-Operative Stomach, Radiology **22**:191 (Feb.) 1934.

101. Truesdale, P. E.: The Pylorus: Observations on Its Musculature, Surg., Gynec. & Obst. **21**:298, 1915.

102. Horwitz, A.; Alvarez, W. C., and Ascanio, H.: The Normal Thickness of the Pyloric Muscle and the Influence on It of Ulcer, Gastroenterostomy and Carcinoma, Ann. Surg. **89**:521 (April) 1929.

103. Mecray, P. M., Jr.; Barden, R. P., and Ravdin, I. S.: Nutritional Edema: Its Effect on the Gastric Emptying Time Before and After Gastric Surgery, Surgery **1**:64 (Jan.) 1937.

104. Barden, R. P.; Ravdin, I., and Frasier, W. D.: Hypoproteinemia as Factor in Retardation of Gastric Emptying After Operations of Billroth I or II Types, Am. J. Roentgenol. **38**:196 (July) 1937.

105. Hoelzel, F., and Da Costa, E.: Experimental Production of Pylorospasm and Gastric Retention in Rats, J. Exper. Med. **57**:597 (April) 1933.

causes of ulcer distress. Trauma to susceptible portions of the intestine often is a factor in the production or the maintenance of an ulcer. Such trauma results from (1) scraping of the gastrointestinal contents against the mucosa and (2) projection of gastrointestinal contents against a particular area of the mucosa. These factors are aggravated by rough food, large meals, long intervals between meals or the production of a nozzle effect by narrowing the lumen, especially of the pyloric sphincter.

Gastric evacuation in health and in disease is apparently more dependent on the character of antral peristalsis and the antral and bulbar pressure gradient and less dependent on the activity of the pyloric sphincter than was indicated by earlier studies. Food in the upper intestine initiates the enterogastric reflex and liberates enterogastrone, thus checking gastric motor and secretory activity. This autoregulation of gastric evacuation reduces the motor drive during evacuation and by decreasing trauma to the area in which most ulcers develop must be significant in preventing the formation of ulcers or in permitting ulcers to heal.

Stagnation of gastric or intestinal contents usually stimulates motor and secretory activity, interferes with the normal dilution and neutralization of gastric juice and thus permits strongly acid material to accumulate. This type of gastric juice can digest even normal gastrointestinal mucosa and produce ulcers. Unless the pyloric sphincter is grossly obstructed, surgical procedures designed to circumvent the sphincter function usually exert but little influence on gastric evacuation.

PATHOGENESIS OF GASTRODUODENAL ULCER

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The problem of the cause of gastric and duodenal ulcer is a part of the more general question of the resistance of the gastrointestinal tract to the digestive action of its own secretions. This was well stated in a thoughtful paper by Joseph Warren [1] more than fifty years ago:

> . . . The question is: Why do organisms which manifest such power of digesting and assimilating the material they require, leave quite intact those organs or tissues where these processes go on so actively? Why does the stomach digest various albuminous substances so readily, and yet fail to attack its own walls, containing substantially the same material? Why do the intestines, with their much more varied power of digestive action, remain undisturbed and uninjured by this activity? Why does the pancreas secrete at least three vigorous ferments, and yet work on unaffected by each and all of them?

John Hunter [2] interested himself in this problem and explained the resistance of the normal gastric wall to digestion on the basis of a vital principle in the following picturesque language:

> . . . If it was possible for an animal to live in the stomach of another animal, supposing digestion not to be going on in that stomach, it would then live while digestion was going on; for that animal would not be in the least dissolved, because the living principle in the animal would prevent or counteract the digestive quality of the stomach. If this was not the case then we might readily suppose that even though the animal life was not immediately affected by the digestive power, yet at last it might be destroyed by the external and extreme parts of the animal being digested, and so the animal be obliged to die, like a person with mortification. But that a living animal will not be so dissolved is every day proved by worms, maggots or flies, living in the stomach of many animals; and if it was a power that could act upon a part that had the living principle, as well as an acid can, then the stomach itself would certainly be dissolved. If one could conceive a man to put his hand into the stomach of a lion, and hold it there without hindering the digestive powers, the hand would not in the least be digested; and if the hand of a dead man was put in at the same time, whether separated or not from the body, that hand would be digested while the other would not.

From the time of Hunter many men have speculated and worked in this field, and the view has steadily gained headway that ulcer of the stomach is in some way due to a local loss of resistance on the part of

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1. Warren, J. W.: Boston M. & S. J. **116**:249, 1887.

2. Hunter, J.: Essays and Observations on Natural History, Anatomy, Physiology, Psychology and Geology, London, J. Van Vooret, 1861, vols. 1-2.

the mucous membrane to the digestant activity of the gastric juice. The widely adopted term "peptic ulcer" is an expression of that view. The occurrence of the lesion in those parts of the alimentary tract that are exposed to gastric juice (viz., the lower part of the esophagus, the stomach, the first portion of the duodenum, the part of the jejunum adjacent to a gastroenterostomy stoma and the part of the ileum adjacent to the entrance of Meckel's diverticulum when this contains gastric mucosa) and nowhere else may be taken as strong confirmatory evidence. However, under normal conditions the mucous membrane is not digested away.

During the past twenty years a great many significant experiments have been done and observations made that have helped to bring into view certain conditions under which chronic progressive ulcer in the stomach and intestines may be expected. As a direct result of planned experimental procedures the disease has been caused to develop in dogs, cats and rats and to duplicate in almost every particular that encountered in man. The gross and histologic appearance of the experimental ulcer exactly resembles the clinical lesion, and it has been observed to perforate, to cause profuse and fatal hemorrhage and to heal under a type of medical management which resembles that found effective in man. It seems likely therefore that an accurate understanding of the alterations in the physiology of the alimentary tract under which experimental ulcer forms and heals should largely clarify the clinical problem.

RESISTANCE TO THE DIGESTIVE ACTION OF THE NORMAL GASTRIC CONTENT BY THE GASTRIC AND THE DUODENAL MUCOSA

The chemical and mechanical traumas produced by the normal gastric content are not sufficient to induce lesions in the normal gastric and duodenal mucosa and prevent them from healing or indeed to delay materially the healing of extensive lesions artificially produced. The prompt healing of the gastric mucosa after the most extensive resections has been commented on by many authors. The earlier literature on ulcer is replete with more or less unsuccessful attempts to produce a chronic progressive lesion in the gastric or duodenal mucosa of the dog or the rabbit. Rapid healing has usually been found to take place when acute lesions of the stomach wall have been produced by the actual cautery, chemical corrosives, excision of large areas of mucosa, ligation or thrombosis of the gastric vessels and the local and intravenous injection of bacterial cultures. This effort has served, however, to make evident the great capacity of the gastric mucosa of these animals to heal in the presence of the usual gastric content even after the most extensive

mechanical and chemical traumas. Bolton,[3] Friedman and Hamburger,[4] Dragstedt and Vaughn,[5] Shapiro and Ivy,[6] Wolfer [7] and others have produced chronic gastric ulcers in dogs by methods which are chiefly serviceable in studying the subsequent effect of this type of trauma on the secretory and motor functions of the stomach but are of doubtful significance in determining the cause of the spontaneous lesions.

RESISTANCE TO THE DIGESTIVE ACTION OF THE NORMAL GASTRIC CONTENT BY OTHER ORGANS

Resistance to the digestive action of the normal gastric content is not limited to the gastric and the duodenal mucosa. As previously noted, Hunter expressed the opinion that all living uninjured cells could resist the digestive action of the gastric content—a statement that at the present time seems to be at least partially true. I [8] have reviewed the earlier literature on this problem, and there is no need for repetition here. The experiments reported in my former paper have been confirmed and amplified in my laboratory in the succeeding years, and the following observations are well supported by numerous experiments. An isolated segment of the duodenum, the jejunum, the ileum or the colon of a dog may be successfully implanted into a defect in the stomach. If the transplant is made in such a way that the mesenteric blood supply is not interfered with and the mucous surface is exposed, the transplant will remain grossly intact and of normal appearance for at least a year; this is evidenced by the work of Fiori,[8] Mann [9] and Dragstedt and Vaughn.[5] In a somewhat similar way the spleen, the kidney or the pancreas of a dog may be mobilized and sutured into a defect in the gastric wall. If this is done with care not to injure the blood supply of the transplant, it will remain undigested for many weeks. The fibrous capsule of the sutured organ may be first removed so that the gastric content has direct access to the parenchyma, and still the tissue is not digested away, but rather in time a thin layer of gastric mucosa grows out from the cut edge and finally covers the surface of the transplant.[10]

3. Bolton, C.: Ulcer of the Stomach, London, Edward Arnold & Co., 1913, p. 386.

4. Friedman, J. C., and Hamburger, W. W.: Experimental Chronic Gastric Ulcer, J. A. M. A. **63**:380 (Aug. 1) 1914.

5. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, Arch. Surg. **8**:791 (May) 1924.

6. Shapiro, P. F., and Ivy, A. C.: Gastric Ulcer: Experimental Production of Gastric Ulcer by Local Anaphylaxis, Arch. Int. Med. **38**:237 (Aug.) 1926.

7. Wolfer, J. A.: Ann. Surg. **84**:89, 1926.

8. Fiori, P.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:239, 1913.

9. Mann, F. C.: J. M. Research **35**:289, 1917.

10. Dragstedt, L. R.: Ann. Surg. **102**:563, 1935.

CAPACITY OF PURE GASTRIC JUICE TO DESTROY ALL LIVING TISSUES

Pure gastric juice has the capacity to destroy and digest all living tissues, including the wall of the stomach itself. A somewhat complicated type of experimental procedure has been required to secure the evidence for this statement. The usual gastric content consists of a mixture of swallowed food and saliva, gastric juice from the parietal cells of the fundus, mucus and a neutral or faintly alkaline secretion from the pyloric antrum and varying quantities of regurgitated duodenal juices. Pure fundus secretion can be obtained by constructing in a dog the Heidenhain or Pavlov accessory stomach pouch or one of the more recent modifications. Larger quantities may be obtained by isolating the entire stomach from continuity with the esophagus and duodenum, either with the vagi severed as in the method of Lim, Ivy and McCarthy [11] or with the vagus innervation preserved as described by Dragstedt and Ellis.[12] Juice is secreted by the isolated pouch or stomach as a result of secretory impulses carried by the vagus nerves where these persist and through the action of the gastric hormone, gastrin, liberated from the stomach or the upper intestine in response to the ingestion of food. The fundus secretion obtained in this way consists almost entirely of a water solution of hydrochloric acid and the enzyme pepsin.[13] The hydrochloric acid is present in an almost constant concentration of about 135 clinical units.

Living tissues have been exposed to the digestant action of this pure undiluted secretion in various ways. Matthews and Dragstedt [14] permitted the secretion from a small Heidenhain or a Pavlov pouch to drain into the jejunum or the ileum instead of to the outside and noted the development of a large progressive perforating ulcer in the intestinal mucosa adjacent to the anastomosis with the accessory stomach. When the implant was made into the ileum, ulcer developed in 100 per cent of the cases, but when the anastomosis was made with the jejunum, the incidence of ulcer was reduced to 85 per cent; this indicates perhaps a greater resistance of the more oral mucosa. In a similar experiment Goldberg [15] prepared a Heidenhain pouch of the stomach and connected it to the exterior by means of a segment of small intestine. Ulcer appeared in the mucosa of the intestinal segment near the anastomosis with the accessory stomach.

Organs such as the spleen, the kidney, the pancreas, the omentum and the intestinal serosa may be subjected to the digestive action of pure

11. Lim, R. K. S.; Ivy, A. C., and McCarthy, J. E.: Am. J. Physiol. **74**:616, 1925.

12. Dragstedt, L. R., and Ellis, J. C.: Am. J. Physiol. **93**:407, 1930.

13. Hollander, F.: J. Biol. Chem. **104**:33, 1934.

14. Matthews, W. B., and Dragstedt, L. R.: Surg., Gynec. & Obst. **55**:265, 1932.

15. Goldberg, S. L.: Ann. Surg. **96**:155, 1932.

gastric juice by implanting them into defects in the walls of isolated Pavlov or Heidenhain accessory stomachs or in totally isolated stomachs. When this is done, the transplant becomes promptly excavated by the digestive action of the gastric juice, and death from hemorrhage takes place in a few days.[10] The contrast with the almost complete immunity from digestion of such tissues implanted into similar defects in normal stomachs is striking and shows that pure gastric juice has a marked aggressive action on living tissue, while the gastric content is relatively inert.

The experimental ulcer in the lower intestine has its counterpart in the ulcer found in the ileum of man opposite the entrance of persisting Meckel's diverticulum. The diverticulum in these cases has been found to contain heterotopic gastric mucosa of the fundus type,[16] and in a recent case in which I performed an operation a fluid acid to litmus was demonstrated in the excised specimen. It is thus certain that this misplaced gastric mucosa can secrete an acid juice, and it is highly probable that the secretion is identical in composition with that from the stomach.

In all of the experiments in which pure gastric juice from an isolated pouch of the stomach is permitted to flow into the lower intestine, the ulcer forms in the intestinal rather than in the gastric mucosa. Since the exposure is similar, one must conclude that the gastric mucosa has the greater resistance to digestion. That this protective capacity is not absolute has been demonstrated clearly by means of the completely isolated stomach in which the secretory vagus innervation has been preserved. Dogs prepared in this way have been under almost continuous observation in my laboratory for the past twelve years.[12] If the alkalosis and the dehydration incident to the total loss of gastric juice are compensated for by the intravenous injection of adequate salt solution, these animals may survive in good condition for many months. They secrete volumes of gastric juice ranging from 1,500 to 2,500 cc. in twenty-four hours with a free acid content of 130 to 140 clinical units and a high pepsin content. In the great majority a large sharply punched-out ulcer develops in the middle portion of the isolated stomach and causes profuse hemorrhage or perforates and produces rapidly fatal peritonitis. The development and the progress of gastric ulcer have been observed by introducing a cystoscope through the external cannula into the cavity of the stomach. The preservation of the secretory fibers of the vagus nerves to the isolated stomach seems to be a matter of some importance in the genesis of the ulcer since Ivy reported that in his extensive experience with the same preparation after the vagi have been severed, no ulcer was found.

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16. Dragstedt, L. R.: Ulcers Acidum of Meckel's Diverticulum, J. A. M. A. **101**:20 (July 1) 1933.

WHY THE GASTRIC WALL IS NOT NORMALLY DIGESTED AWAY

Under normal conditions the gastric wall is not digested away because it is not exposed to pure gastric juice. This conclusion follows from a consideration of the experimental evidence just presented and of those factors which normally regulate the secretions of the stomach. Carlson [17] found that the empty stomach of the average healthy young adult man when aspirated in the morning before breakfast contained usually less than 50 cc. of fluid, often bile stained and with no free acid or at most only slight amounts. The normal stimuli for gastric secretion, such as the sight, the odor and the taste of food, are followed so promptly by its ingestion that the secretion from the fundus is largely diluted and neutralized. The secretion of gastric juice dependent on the chemical mechanism occurs in response to the presence of food in the stomach or the upper intestine, and the rate of secretion falls off rapidly when the stomach becomes empty. It is thus evident that food, which in normal persons is the stimulus for the formation of gastric juice, is also the chief factor which protects the tissues against its corrosive activity.

A continuous secretion of gastric juice occurs which is apparently not dependent on psychic stimuli or the presence of food in the stomach. The volume of this secretion appears to be slight as compared with the large amounts called forth in response to the taking of food. While the initial acidity of this juice is probably comparable with that of the food-stimulated secretion, the small volume permits almost complete neutralization by the mucus of the pyloric antrum, swallowed saliva and possibly also regurgitated duodenal juices. It is conceivable that this neutralizing mechanism may fail or prove inadequate in various ways and that as a result more or less pure gastric juice may accumulate in the stomach empty of food. It seems probable that some abnormality of this type is responsible for most of the cases of ulcer in man.

FAILURE IN THE MECHANISM OF NEUTRALIZATION AS A CAUSE OF ULCER

Does a failure in the mechanism for the neutralization of gastric juice cause ulcer? As pointed out before, in healthy persons gastric juice appears to be secreted by the fundus mucosa at a constant acidity in the neighborhood of 135 clinical units. While food is probably the most important neutralizing factor, a considerable body of evidence has accumulated which indicates that other factors are important, and it is, of course, on these that the whole burden falls if excessive secretion occurs in the absence of the taking of food. The work of Mann and associates published in 1923 [18] must be credited largely with establishing

17. Carlson, A. J.: Physiol. Rev. **3**:1, 1923.
18. Mann, F. C., and Williamson, C. S.: Ann. Surg. **77**:409, 1923.

the importance of the neutralizing effect of the duodenal juices in preventing the development of ulcer in the duodenum. Mann and co-workers accomplished this by demonstrating that diversion of the bile, the pancreatic and the duodenal juice into the lower ileum by their procedure of internal duodenal drainage produced progressive perforating ulcers in the part of the intestine adjacent to the pylorus in 95 per cent of the cases. Before this work similar evidence had been presented by Exalto in 1911 [19] and Langenskiöld in 1913.[20] Mann's striking experiments stimulated a large number of studies on the relative importance of each of the three duodenal juices in this protective action. While most of this evidence falls in line with the concept that the effect can be attributed to the capacity of these secretions to neutralize the gastric acid, some apparently contradictory results have been obtained.

Effect of the Exclusion of Bile from the Upper Intestinal Tract.—Bile has been excluded from the duodenum in experimental animals by diverting it to the outside by various types of external fistula, by diverting it into the pelvis of the kidney, from which it passes out in the urine, by diverting it into the lower intestine or the colon, and by completely and permanently occluding the bile ducts.[21] The results of these procedures with respect to the incidence of ulcer in the duodenum vary widely. Complete obstruction to the bile ducts with resultant jaundice and hepatic cirrhosis leads to the development of typical progressive ulcers in the duodenum in the great majority of animals so prepared. On the other hand, certain kinds of external biliary fistula may divert the bile from the duodenum for many months without causing ulceration. Thus during the past five years in my laboratory I have observed 15 dogs provided with total biliary fistulas survive for periods of six to fifteen months and at death display no evidence of ulcer in the stomach or the duodenum. In these animals the common bile duct was doubly ligated and divided, and a large gold-plated cannula was placed in the fundus of the gallbladder. This cannula was then carefully wrapped with part of the omentum and led outward through a stab wound in the abdominal wall. Bile was collected in rubber bags tied to the cannula. It is possibly of considerable importance that no obstruction to the free escape of bile exists with this type of fistula, that ascending infection does not occur and that the liver remains grossly and histologically

19. Exalto, J.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:13, 1911.

20. Langenskiöld, F.: Skandinav. Arch. f. Physiol. **31**:1, 1913.

21. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcers: Experimental Study, Arch. Surg. **20**:997 (June) 1930. Andrews, E.: Personal communication to the author. Kapsinow, R.: Ann. Surg. **83**:614, 1926. Blanck, E. E.: Surg., Gynec. & Obst. **61**:480, 1935. Bollman, J. L., and Mann, F. C.: Peptic Ulcer in Experimental Obstructive Jaundice, Arch. Surg. **24**:126 (Jan.) 1932.

normal. It seems possible that the varying incidence of ulcer reported after external biliary fistula by the Rous and McMaster technic or after anastomosis of the gallbladder to the ileum, the colon or the pelvis of the kidney following occlusion of the common duct may be due in part to the factors of partial obstruction or ascending infection. The probability that damage to the liver is important in the genesis of some of these ulcers resulting from biliary fistula is further supported by the observations of Bollman and Mann [22] that chronic duodenal ulcers occasionally appear in animals with Eck fistula as well as after the administration of cinchophen.[23] This question of the relation of damage to the liver to gastroduodenal ulcer should receive further study.

Effect of the Exclusion of Pancreatic Juice from the Upper Intestinal Tract.—Pancreatic juice has been excluded from the duodenum of the dog by various types of external pancreatic fistula, by the implantation of the ducts into the lower intestine, by ligation of the ducts and by total pancreatectomy. Here again the results vary widely. Partial exclusion of the pancreatic juice has been produced by a great many workers from the time of De Graaf by cannulating or implanting the lower, larger pancreatic duct of the dog into the abdominal wall. Ulcer in such animals rarely develops. When Elman [24] cannulated this duct by the Rous and McMaster method after first ligating the other ducts, he secured a much greater volume of pancreatic juice and observed ulcer in the duodenum.

The failure to obtain ulcer in the duodenum by producing an external fistula of the lower pancreatic duct in the dog is undoubtedly due to the fact that in this preparation the major portion of the pancreatic secretion still finds its way into the duodenum. This is illustrated by the occurrence of ulcer in almost 100 per cent of the animals from which the entire secretion is drained to the outside by the type of fistula described by Dragstedt, Montgomery and Ellis.[25] Since that report, more than a hundred such fistulas have been prepared in the laboratory in connection with various problems. The principle of the method has remained to produce an isolated sac of that small portion of the duodenum receiving the pancreatic ducts and to lead the juice from this sac to the outside by means of a gold-plated cannula wrapped in omentum. The continuity of the alimentary tract may be reestablished by end to end

22. Bollman, J. L., and Mann, F. C.: Chronic Duodenal Ulcer in Animals with Fistulas on Certain Diets, Arch. Path. **4**:492 (Sept.) 1927.

23. Stalker, L. K.; Bollman, J. L., and Mann, F. C.: Am. J. Digest. Dis. & Nutrition **3**:822, 1937.

24. Elman, R.: J. Clin. Investigation **10**:183, 1931.

25. Dragstedt, L. R.; Montgomery, M. L., and Ellis, J. C.: Proc. Soc. Exper. Biol. & Med. **28**:109, 1930.

anastomosis of the divided duodenum or by the method originally described. These animals die rapidly of dehydration and acidosis unless the sodium lost in the pancreatic juice is replaced by parenteral injection. When this is done, life is greatly prolonged, but almost inevitably a progressive ulcer develops in the duodenum which causes death from hemorrhage or perforation. The occurrence of these ulcers may be prevented or at least delayed by the oral administration of calcium carbonate and powdered bone meal, but so far I have been unable to cure an ulcer already formed.

Permanent occlusion of the pancreatic ducts is best accomplished by doubly ligating and dividing the ducts, separating the pancreas completely from the duodenum and interposing the omentum between. Under such conditions the pancreas degenerates in a few months to a thin fibrous cord which on microscopic examination is found to consist of islets with small remnants of acinous tissue. No pancreatic juice whatever enters the duodenum; the animals lose weight, and the bulky stools associated with pancreatic insufficiency appear. Nevertheless, in a series of 17 animals operated on in this fashion in my laboratory ulcer developed in only 5—an incidence of 29 per cent. This incidence agrees fairly well with that reported by other investigators. Of course complete removal of the pancreas provides for the total absence of pancreatic juice in the duodenum, and it is in this case that the greatest discrepancy in the incidence of ulcer is found. During the past seven years over 300 pancreatectomized dogs have been studied in my laboratory for periods ranging from a few months to over two years. All these animals were carefully examined post mortem, and of this large number only 4 presented duodenal or gastric ulcer. These animals were fed the usual diet of bread, meat, milk and vitamin supplements but were not given alkalis in any form. Why does ulcer develop in the dog with a total pancreatic fistula in 100 per cent of the cases, while the animal whose pancreas has been removed remains almost immune? I cannot answer this question, and it suggests that the problem is not entirely one of failure of neutralization of the gastric acid by the sodium bicarbonate of the pancreatic juice.

Effect of Exclusion of Duodenal Juice from the Upper Intestine.—Exclusion of the duodenal juice may be accomplished by extirpation of the duodenum, an operation that was first demonstrated to be compatible with life by my associates and me in 1918.[26] In these experiments, although both bile and pancreatic juice also were excluded, ulcer was not observed. In 1922, Mann and Kawamura [27] reported the successful

26. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: Am. J. Physiol. **46**:584, 1918.

27. Mann, F. C., and Kawamura, K.: Ann. Surg. **75**:208, 1922.

removal of the duodenum in experiments on dogs, cats and hogs; the jejunum was anastomosed to the pylorus, and the bile and the pancreatic ducts were implanted into the jejunum. In 2 of the 11 dogs on which this operation was performed, jejunal ulcer appeared and caused death by perforation. While this is the best experiment on the role of the duodenal juice, there remains even here the possibility that the implantation of the bile duct may have caused some obstruction and damage to the liver.

A consideration of the data, a portion of which has been summarized, indicates that it is perhaps safe to conclude that absence of pancreatic juice, bile and duodenal juice or possibly of any one of these secretions from the upper intestine may be expected to cause a progressive perforating ulcer in the duodenum. While the nature of the protective action of these secretions is not entirely settled, it is likely that protection is in part due to the neutralization of the hydrochloric acid of the gastric juice. In each case the effective substance is probably sodium bicarbonate, and its greater concentration in pancreatic juice probably makes this secretion the most important. There is no evidence, however, and little likelihood that absence of these secretions or reduction in their neutralizing properties is responsible for ulcer in man except in rare instances, as in the case reported by Morton.[28] The disease is one that commonly affects young and otherwise healthy adults without the usual symptoms and findings of biliary or pancreatic insufficiency.

The report of Anderson and Fogelson [29] that a relative decrease in the gastric mucin occurs in some patients with duodenal ulcer is interesting, and it is possible that a defect of this type in the neutralizing mechanism may be important. Further studies should be made.

EXCESSIVE CONTINUOUS SECRETION OF GASTRIC JUICE IN THE EMPTY STOMACH AS A CAUSE OF ULCER IN EXPERIMENTAL ANIMALS

As indicated in the preceding section, it seems unlikely that pancreatic juice, bile and succus entericus fail to reach the duodenum and that the absence of these secretions can account for any large number of ulcers in man. There remains, however, the possibility that an excessive volume of gastric juice might exhaust the neutralizing mechanism of the stomach and the duodenum and then attack the mucosa. An excessive secretion in the empty stomach should be especially dangerous since the buffering effect of the food is ordinarily so effective. Attempts have been made to provoke such a secretion in animals both by stimulating the secretory

28. Morton, C. B., and Graham, J. B.: Ann. Surg. **91**:73, 1930.
29. Anderson, R. K., and Fogelson, S. J.: J. Clin. Investigation **15**:169, 1936.

nerves in the vagi and by the use of histamine. In 1927, Silbermann [30] reported the occurrence of ulcer in the stomach and duodenum of dogs subjected to repeated sham feeding experiments. Double esophagostomy was performed on 23 dogs, and feeding was accomplished through the peripheral esophageal opening. These dogs were allowed to eat for forty to sixty minutes three times a day, the swallowed food escaping to the outside via the fistula. Ulcer developed in the stomach in every case in fourteen to forty-nine days. Similar sham feeding experiments were performed by Schmidt and Fogelson [31] and in my laboratory; however, the results were negative; no ulcer appeared. Büchner, Siebert and Malloy [32] reported the occurrence of ulcer in the stomach of rats after the repeated injection of histamine. Bürkle-de la Camp [33] found that the healing of acute ulcer produced by the injection of silver nitrate beneath the gastric mucosa of dogs was markedly delayed by the repeated injection of histamine, a finding subsequently confirmed by Flood and Howes.[34] The recent work of Walpole, Varco, Code and Wangensteen [35] is especially interesting and important. These workers secured continuous stimulation of the gastric glands by Code's method of implanting pellets of histamine mixed with beeswax into the muscles or beneath the skin. A copious continuous secretion of gastric juice resulted; this result could be obtained daily for long periods. Typical chronic perforating ulcer appeared in the stomach or the duodenum of all the common laboratory animals so treated.

EXCESSIVE CONTINUOUS SECRETION OF GASTRIC JUICE IN THE EMPTY STOMACH AS A CAUSE OF ULCER IN MAN

The demonstration that excessive secretion of qualitatively normal gastric juice will produce ulcer in the stomach and duodenum of lower animals is obviously of the greatest significance from the standpoint of the clinical problem. No one can deny that the same effect would in all probability be produced in man were the experiment carried out. Further, there is plenty of evidence that an excessive volume of gastric juice is secreted by many, perhaps most, patients with ulcer, although the cause of the hypersecretion is unknown. The early gastroenterolo-

30. Silbermann, I. S.: Zentralbl. f. Chir. **54**:2385, 1927.

31. Schmidt, C. R., and Fogelson, S. J., cited by Fogelson, S. J.: Internat. Abstr. Surg. **65**:1, 1937; in Surg., Gynec. & Obst., July 1937.

32. Büchner, F.; Siebert, P., and Malloy, P. J.: Beitr. z. path. Anat. u. z. allg. Path. **81**:391, 1928.

33. Bürkle-de la Camp, H.: Deutsche Ztschr. f. Chir. **220**:31, 1929.

34. Flood, C. A., and Howes, E. L.: Surg., Gynec. & Obst. **58**:136, 1934.

35. Walpole, S. H.; Varco, R. L.; Code, C. F., and Wangensteen, O. H.: Proc. Soc. Exper. Biol. & Med. **44**:619, 1940.

gists noted that the stomach contents of patients with ulcer after an Ewald test meal were more acid than those of normal people, and the concept of hyperacidity as a cause of ulcer arose. When Carlson pointed out that this acidity approached but did not exceed the acidity of pure normal gastric juice, the idea of a pathologic hyperacid gastric juice had to be abandoned in favor of the concept of hypersecretion of normal juice with deficient neutralization. On the basis of present information it seems likely that the patient with ulcer secretes more gastric juice in response to food taking than the normal person and also, what is perhaps more important, that he secretes more gastric juice when there is no obvious stimulant. This fact is illustrated in an observation I made several years ago and has been noted also by others. In several patients with duodenal ulcer, the stomach was lavaged in the evening to remove all traces of food, and constant aspiration was maintained all night to recover as much of the continuous secretion as possible. From 500 to 1,200 cc. of clear fluid was obtained with free acid that in 1 case reached 90 clinical units. Since this juice was obtained when the upper gastrointestinal tract was empty of food and the patient was asleep, it is clear that the usual stimuli (nervous and chemical) were not operating. Under similar conditions, normal persons yielded usually less than 300 cc. of secretion with free acid rarely above 50 clinical units and often entirely absent.

What is the cause of this excessive continuous secretion of gastric juice? Is it due to the continuous formation and absorption of gastrin or histamine into the blood stream or does it depend on abnormal activity of the nervous secretory mechanism? These questions remain unanswered, but there are various possibilities that may be explored.

The occurrence of acute ulcers in the duodenum and the stomach after extensive superficial burns (Curling's ulcer) is, according to Harkins,[36] more common than coincidence would allow. Can these ulcers in man be attributed to the absorption of histamine or similar products from the burned area in a manner analogous to that of the experimental histamine ulcers of Walpole, Varco, Code and Wangensteen? This possibility certainly must be considered, and studies should be made on the continuous secretion of gastric juice in patients with severe burns as well as on experimental animals. The allergic states represent another condition in which liberation of histamine in the body fluids occurs [37] and might therefore conceivably affect gastric secretion. Studies on the incidence of ulcer and on the continuous gastric secretion in such patients might yield interesting data.

36. Harkins, H. N.: Surgery **3**:608, 1938.

37. Dragstedt, C. A.: Physiol. Rev. **21**:563, 1941.

THE RELATION OF THE NERVOUS SYSTEM TO GASTRODUODENAL ULCER

While the possibility of continuous absorption of gastric secretory stimuli, such as histamine, must be admitted as a cause for the hypersecretion in patients with ulcer, the view that the hypersecretion is due to abnormal activity of the vagus secretory mechanism seems more attractive at present. For a number of years many investigators have commented on the high incidence of ulcer in those persons whose occupations involve unusual anxiety, stress and strain and on the tendency for healed ulcers to recur during periods of great mental and emotional tension. Cushing [38] marshaled a good deal of evidence implicating disturbances in the central nervous system as a causative factor in ulcer and reported the occurrence of acute perforating ulcer in the stomach after operation for cerebellar tumor. Similar cases have been reported by Grant.[39] The central nervous system affects the gastrointestinal tract by causing variations in the tract's blood supply, motility and secretions. The concept that irritative lesions in the brain produce ulcer in the stomach through local vasoconstriction and anemia in the mucous membrane lacks experimental support. Attempts to produce ulcer by extensive ligation of gastric blood vessels have usually failed. Disturbances in motility, particularly pylorospasm, which may cause retention and prevent the regurgitation of the neutralizing juices of the duodenum into the stomach, seems to merit more consideration. However, on the basis of the available experimental evidence on the genesis of ulcers, a portion of which has been summarized in this paper, it seems most probable that the central nervous system plays an undoubted role in causing the disease through increasing the volume of gastric secretion. The patient with ulcer who secretes large amounts of gastric juice at night is commonly the young adult who presents the stigma of excessive nervous tension. The acute ulcers in the stomach and duodenum which have been reported following various intracranial operations might well be due to the secretion of acid gastric juice in the empty stomach brought on by stimulation of the gastric secretory centers as a result of the brain tumor itself or of operative trauma. Several years ago I had an opportunity to study the gastric contents of 3 patients during the first two or three days following their operations for brain tumor and to compare these findings with those obtained from patients after operations within the abdomen. In the cases of the latter, the contents secured by continuous aspiration were commonly mixed with duodenal secretions and were neutral or only slightly acid in reaction. In sharp contrast the patients who had had intracranial operations yielded from 400 to 1,100 cc.

38. Cushing, H.: Surg., Gynec. & Obst. **55**:1, 1932.

39. Grant, F. C.: Ann. Surg. **101**:156, 1935.

per day of typical gastric juice with a high free acid content (80 to 110 clinical units). These findings require confirmation by a more extensive study, since, if true, they suggest that some type of medical management for ulcer should be instituted after operation on the central nervous system.

Section of the vagus nerves has been suggested and carried out a number of times for the treatment of duodenal ulcer. The literature in this field has been reviewed by Hartzell.[40] He found that in dogs the acidity of the gastric secretion in response to the ingestion of food was markedly reduced, particularly when the vagi were divided above the diaphragm. The effect of this operation on the continuous secretion seems not to have been investigated. Information of this kind, especially in cases of duodenal ulcer with marked hypersecretion, should be of the greatest importance.

SUMMARY

The chemical and mechanical traumas produced by the normal gastric content are not sufficient in themselves to cause ulcers in the normal gastric and duodenal mucosa and prevent them from healing or to delay materially the healing of extensive lesions artificially produced. This resistance to the digestive action of the normal gastric content is moreover not limited to the gastric and the duodenal mucosa but is displayed to a considerable extent also by such organs as the spleen, the kidney and the pancreas. Pure gastric juice, on the other hand, can destroy and digest all living tissues, including the wall of the stomach itself. In this effect the gross and the histologic appearance of the typical progressive ulcer and the associated gastritis in man are exactly reproduced in the experimental animal. Under normal conditions, the gastric wall is not digested away because it is not exposed to pure gastric juice. Food, which in the normal person is the stimulus for the formation of gastric juice, is also the chief factor which protects the tissues against its corrosive activity. Pancreatic juice, gastric and intestinal mucus, duodenal juice and bile (probably in the order named) constitute an additional mechanism which protects the duodenal and, to a certain extent, also the gastric and the jejunal mucosa. When excessive volumes of normal gastric juice are continuously secreted in experimental animals, this defensive neutralizing mechanism is overcome, and ulcer is produced. It is probable that in man a similar excessive secretion of gastric juice often occurs, and ulcer results. It seems likely that in most cases this hypersecretion is neurogenic and is abnormal in the sense that it operates when the stomach is empty and in the absence of the usual stimuli for gastric secretion.

40. Hartzell, J. B.: Am. J. Physiol. **91**:162, 1929.

PEPTIC ULCER AND GASTRIC SECRETION

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The role of the digestive action of gastric juice in the problem of peptic ulcer has long been recognized by clinicians; this is evident from the use of such descriptive terms as "peptic," "erosive," "corrosive" and "digestive." The originator of this concept is not known, but possibly the thought came to Matthew Baillie, to John Abercrombie and to Cruveilhier also, for John Hunter had already (1778) raised the question of why the normal stomach does not digest itself. The theory was developed further during the nineteenth century, particularly during the latter half, and in 1910, Schwarz [1] enunciated his now famous and much disputed doctrine of "no acid—no ulcer." The purpose of the present paper is to discuss the present status of the subject and the therapeutic implications. Time and usage have apparently justified the selection of the term "peptic ulcer" to denote a specific lesion appearing in various definite locations along the digestive tube and possessed of a rather characteristic structure. The "peptic ulcers" of the esophagus, the stomach, the duodenum, the jejunum or the ileum do not essentially differ anatomically, or indeed functionally, from one another. Even the distinctions between acute, subacute and chronic lesions are not sharp. Konjetzny,[2] in his beautiful anatomic study, has clearly traced the transition from acute erosion to acute ulcer and thence to chronic ulcer. From a practical point of view, erosion and truly acute ulcer are of little importance for they heal quickly and usually produce few or no symptoms. The subacute and chronic lesions are more likely to produce clinical manifestations and hence are the ulcers to be primarily considered.

GASTRIC SECRETION IN RELATION TO PEPTIC ULCER

The most comprehensive statistical analysis of gastric secretion was that made by Vanzant and associates.[3] These workers found that "there

From the Frank Billings Medical Clinic, Department of Medicine, the University of Chicago.

1. Schwarz, K.: Ueber penetrierende Magen- und Jejunalgeschwüre, Beitr. z. klin. Chir. **67**:96, 1910.

2. Konjetzny, G.: Die entzündliche Grundlage der typischen Geschwürsbildung im Magen und Duodenum, Berlin, Julius Springer, 1930, p. 80.

3. Vanzant, F. B.; Alvarez, W. C.; Eusterman, G. B.; Dunn, H. L., and Berkson, J.: The Normal Range of Gastric Acidity from Youth to Old Age: An Analysis of 3,746 Records, Ann. Int. Med. **49**:345, 1932.

was an increase of approximately 12 units of free acidity in the case of duodenal ulcer . . . In the case of gastric ulcer the mean free acidity was lower than normal by about 6 units . . . The incidence of achlorhydria was half of that observed in normal persons." (The test meal consisted of eight arrowroot cookies and 400 cc. of water.) In terms of response to any standard test meal, it has become clear that the gastric acidity in patients with peptic ulcer falls within the normal range, in that presumably normal persons with gastroscopically normal gastric mucosas may exhibit variations from no free acidity to values of 140 to 160 clinical units. In this sense, it is incorrect to speak of hypoacidity and hyperacidity or of hyposecretion and hypersecretion; almost anything is normal.[4] Peptic ulcer occurs in persons with a low secretory rate as well as in those with a high secretory rate. Chronic peptic ulcer does not occur, however, in patients with complete and persistent achlorhydria—a subject to be discussed in detail later. In terms of response to a standard test meal, the secretory capacity of the stomach seems to be the same during the periods of quiescence and healing as it is during periods of activity.[5] The secretory response to a test meal, even one containing histamine, probably does not measure or give a good indication of the total twenty-four hour secretion or, what is perhaps even more important, of the nocturnal so-called fasting or basal secretion. Clinicians have long been aware of the fact that the excessive continued night secretion constitutes one of the greatest difficulties in therapy. Sippy,[6] Henning and Norpoth,[7] Winkelstein,[8] Palmer,[9] Val Dez[10] and others have shown that, as a rule, patients with ulcer do have a nocturnal secretion which exceeds in amount and acidity that observed in normal persons under similar

4. Carlson, A. J.: The Secretion of Gastric Juice in Health and Disease, Physiol. Rev. **3**:1, 1923. Heintz, E. L., and Welker, W. H.: Acidity Curves in Gastric, Duodenal and Mixed Ulcers, Ann. Int. Med. **3**:371, 1924.

5. Brown, C. F. G., and Dolkart, R. E.: Gastric Acidity During Recurrences and Remissions of Duodenal Ulcer, Arch. Int. Med. **60**:680 (Oct.) 1937.

6. Sippy, B. W.: Gastric and Duodenal Ulcer, J. A. M. A. **64**:1625 (May 15) 1915; Ulcer of the Stomach and Duodenum, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1921, vol. 3, p. 153.

7. Henning, N., and Norpoth, L.: Untersuchungen über die sekretorische Funktion des Magens während des nächtlichen Schlafes, Arch. f. Verdauungskr. **53**:64, 1933.

8. Winkelstein, A.: One Hundred Sixty-Nine Studies in Gastric Secretion During the Night, Am. J. Digest. Dis. **1**:778, 1935.

9. Palmer, W. L.: Fundamental Difficulties in the Treatment of Peptic Ulcer, J. A. M. A. **101**:1604 (Nov.) 1933.

10. Val Dez, F. C.: The Night Secretion of Free Hydrochloric Acid in the Stomach, Illinois M. J. **81**:149, 1942.

conditions. Wolfson and Wanowskaja [11] found that the hourly secretion of patients with ulcer was definitely and distinctly higher than that observed in normal persons. Bloomfield [12] observed that in terms of response to the histamine test the gastric secretion in patients with ulcer does not differ from that of normal persons but that there is a tendency toward a higher basal secretion. "Certain people, usually with duodenal ulcer, secrete under basal conditions a larger volume of gastric juice of higher acidity than is ever attained in normal asymptomatic individuals." There is thus abundant evidence that as a rule the gastric secretion in patients with peptic ulcer exceeds in amount secreted per hour and per twenty-four hours that found in normal persons.

PATHOGENESIS OF PEPTIC ULCER

In the studies of the pathologic anatomy of peptic ulcer mentioned before, Konjetzny presented satisfactory evidence that the lesion begins in the mucosa, that it increases in size and in depth by invasion and that it is definitely a penetrative process. Experimentally, Mann [13] and numerous other workers [14] have shown conclusively that the ulcer produced by them in diverse ways is also a penetrative invasive process identical in pathologic appearance, and indeed, in behavior, with peptic ulcer as seen in human beings.

The presence of acid gastric juice is essential for the production of such lesions. Indeed, it seems to be the one indispensable factor. "It should again be emphasized that chronic peptic ulcer has only been produced consistently experimentally by methods which prevent the neutralization, dilution or buffering of the gastric content as it passes from the stomach."[13] This statement was made prior to the production

11. Wolfson, A. S., and Wanowskaja, R. L.: Untersuchungen der Magenfunktionen bei Ulkuskranken, Arch. f. Verdauungskr. **61**:191, 1937.

12. Bloomfield, A. L.: The Problem of Gastric Hyperacidity, Am. J. Digest. Dis. **6**:700, 1939.

13. Mann, F. C., in Eusterman, G. A., and Balfour, G. C.: The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1936, p. 57.

14. (*a*) Code, C. F., and Varco, R. L.: Chronic Histamine Action, Proc. Soc. Exper. Biol. & Med. **44**:475, 1940. Hay, L.; Lynn, D., and Wangensteen, O. H.: The Production of Gastric and Duodenal Ulcer in Various Animals by the Intramuscular Implantation of Histamine in Beeswax, Tr. Am. Soc. Exper. Path., 1941, p. 12. Varco, R. L.; Code, C. F.; Walpole, S. H., and Wangensteen, O. H.: Duodenal Ulcer Formation in the Dog by Intramuscular Injections of a Histamine Beeswax Mixture, Am. J. Physiol. **133**:P475, 1941. Walpole, S. H.; Varco, R. L.; Code, C. F., and Wangensteen, O. H.: Production of Gastric and Duodenal Ulcers in the Cat by the Intramuscular Implantation of Histamine, Proc. Soc. Exper. Biol. & Med. **44**:619, 1940. (*b*) Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **55**:265, 1932.

by Code, Varco, Wangensteen and co-workers [14a] of typical chronic peptic ulcer in the dog and other animals as a result of continued hypersecretion induced by the injection of a slowly absorbable mixture of histamine and beeswax. Mann, however, had produced experimental ulcer by means of a continuous drip of hydrochloric acid into the stomach. Büchner and associates [15] produced acute lesions in the stomach of the rat by the subcutaneous injection of histamine and confirmed the observations of Silbermann [16] on the production of acute lesions in the dog by sham feeding. The paramount importance of acid in the production of experimental peptic ulcer thus seems inescapable. Pepsin greatly facilitates the process, but it alone will not destroy the mucosa. The chief protection against the acid attack on the cells of the mucosa seems to be provided by the thin layer of mucus with which they are covered. If this is wiped or rubbed away or dissolved, the cells are bathed in a medium containing a destructively high hydrogen ion concentration, together with the proteolytic enzyme, pepsin. Under such circumstances, ulcer develops. Factors such as thrombosis, embolism and infection are not essential features of experimental ulcer.

There is abundant clinical evidence that with ulcer in human beings the problem is also one of tissue resistance versus acid attack. It is well established that peptic ulcer occurs only in those portions of the digestive tract exposed to the action of acid gastric juice, i. e., the lower esophagus, the stomach, the first and second portions of the duodenum and, after gastroenterostomy, in the portions of the bowel adjacent to gastroenterostomy openings. Primary ulcer of Meckel's diverticulum and solitary peptic ulcer of the small bowel have been shown to occur adjacent to aberrant acid-secreting gastric mucosa.[17] The constancy of this anatomic relation between peptic ulcer and gastric glandular tissue seems to be a thoroughly established pathologic fact.

The second important clinical observation is the occurrence of chronic peptic ulcer in only those persons whose gastric mucosa is able to secrete acid gastric juice. The erroneous concept that chronic peptic ulcer may occur with complete achlorhydria is based largely on informa-

15. Büchner, F.; Siebert, F., and Molloy, P. J.: Ueber experimentelle erzeugte akute peptische Geschwüre des Rattenvormagens, Beitr. z. path. Anat. u. z. allg. Path. **81**:391, 1928. Büchner, F.: Die Pathogenese der peptischen Veränderungen, Jena, Gustav Fischer, 1931.

16. Silbermann, I. S.: Experimentelle Magen-Duodenalulcuserzeugung durch Scheinfüttern nach Pavlow, Zentralbl. f. Chir. **54**:2385, 1927.

17. Brown, P. W., and Pemberton, J. de J.: Solitary Ulcer of Ileum and Ulcer of Meckel's Diverticulum, Ann. Int. Med. **9**:1684, 1936. Fleet, G. A.: Misplaced Gastric Mucosa as a Cause of Massive Rectal Hemorrhage, Canad. M. A. J. **42**:216, 1940. Johnston, L. B., and Renner, G.: Peptic Ulcer of Meckel's Diverticulum, Surg., Gynec. & Obst. **59**:198, 1934. Taylor, A. L.: Epithelial Heterotopias of Alimentary Tract, J. Path. & Bact. **30**:415, 1927.

tion gained from the old Ewald test meal or the fractional meal. The inadequacy of such criteria was shown in 1926.[18] At that time, in a study of the records of 1,004 cases of proved peptic ulcer, satisfactory proof of achlorhydria was found in only 1 case, and in this instance at autopsy the ulcer was found to be healed. Since then, in approximately 2,500 cases of peptic ulcer, I have failed to find a single case of active chronic peptic ulcer with complete and permanent anacidity. Occasionally one sees a patient with a definite bilateral deformity of the duodenal bulb, a typical ulcer deformity, without roentgen evidence of an active ulcer crater, without ulcer symptoms and with histamine-achlorhydria. One such patient seen by me in 1933 gave a history of distress suggestive of ulcer dating from 1923 to 1925 or 1926. In the subsequent seven or eight years there had been apparently no distress of this sort. There are rare cases of pernicious anemia in which an ulcer deformity of the duodenal bulb is found by roentgen examination, but in no such instance coming to my attention has there been evidence, clinical or roentgenologic, of active ulcer. In 1940, Nutter and I[19] analyzed the alleged cases of chronic ulcer with achlorhydria reported by others and found that none of them fulfilled the requirements stipulated in 1926. In a series of 84 cases of chronic gastric ulcer studied by us, there was no instance of achlorhydria. One patient, however, was of great interest because the maximum free acidity (histamine) was only 18 clinical units. Two cases were of considerable interest because of marked fluctuations in gastric secretion, the maximum free acidity (histamine) ranging from 0 to 75 and 79 degrees.

The importance of carrying out repeated histamine tests with careful technic in cases of achlorhydria, including the use of fluoroscopy to check the position of the tip of the tube in the stomach, is illustrated by a case in which four consecutive histamine tests of gastric secretion on June 15, 18, 24 and 25 all failed to disclose free acidity, and yet on June 30, abundant secretion was found, the free acidity reaching a peak of 76 units.[19]

Recently there has come to my attention, through the courtesy of Dr. Sidney Portis, detailed information of another apparent case of gastric ulcer with achlorhydria.

The patient, a man 64 years of age whose symptoms were epigastric distress of two months' duration with a loss of weight of 16 pounds (7.3 Kg.), was referred by Dr. Portis to Dr. Rudolf Schindler for gastroscopic examination on Aug. 17, 1939. Dr. Portis reported that the roentgen examination had disclosed a small lesion of the lesser curvature and the posterior wall of the stomach. An Ewald test meal on August 9 had disclosed no free acid and a total acidity of 18.

18. Palmer, W. L.: Mechanism of Pain in Gastric and Duodenal Ulcer: I. Achlorhydria, Arch. Int. Med. **38**:603 (Nov.) 1926.

19. Palmer, W. L., and Nutter, P. B.: Peptic Ulcer and Achlorhydria: A Further Study of the Role of Acid Gastric Juice in the Pathogenesis of Peptic Ulcer, Arch. Int. Med. **65**:499 (March) 1940.

On August 10, using a fractional Ewald test meal followed with histamine, Dr. Portis found the values listed in table 1. The gastroscopic examination disclosed a "large ulcer of the upper portion of the posterior wall, most likely carcinoma, type 3." The patient underwent operation at the Mayo Clinic on September 6; "a subacute hemorrhagic inflammatory ulcer" was found. No evidence of malignant change was noted in the sections.

This would appear to be satisfactory evidence of peptic ulcer with achlorhydria, yet the existence of persistent achlorhydria is not proved. The fallacy in this case is illustrated by the instance cited before in which four consecutive tests during an interval of ten days failed to disclose free acid, and yet abundant acid secretion was found a few days later.

Chronic peptic ulcer does occur, however, in patients with a low grade secretion. This is shown in table 2 in which are shown the results of protracted studies carried out on a patient under observation

TABLE 1.—*Free and Total Acidity in an Apparent Case of Gastric Ulcer with Achlorhydria After an Ewald Test Meal Followed with Histamine*

Time (A.M.)	Free Acidity	Total Acidity
9:50	0	15
10:05	0	16
10:20	0	16
10:35	0	20
10:50 (histamine injected)	0	26
11:05	0	25
11:20	0	25

for almost six years. The patient, A. K., a woman, was born in 1873. The ulcer, when present, was invariably located on the lesser curvature of the stomach just above the angulus.

It is clear that in this case gastric ulcer recurred at intervals in a stomach with an extremely low secretory response to histamine. The question naturally arises as to whether the gastric juice in such a stomach interfered with the healing of the ulcer or played any role in causing recurrence. Obviously, hyperacidity was not present, and the secretion was considerably less than that ordinarily seen in normal persons. It may be that the resistance or the protection of the mucosal cells was unusually poor, with the result that even this gastric juice was sufficiently destructive to interfere with healing. On Dec. 6, 1939, when the maximum titratable free acidity in response to histamine was only 13 units, the p_H reading was 2.99. This is a hydrogen ion concentration adequate for the conversion of pepsinogen to pepsin. The optimum p_H for peptic activity, according to Hawk and Bergeim,[20] is between 2 and 3. "At about p_H 5 its power to digest protein disappears."

20. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1927.

TABLE 2.—*Summary of a Study of a Patient with Gastric Ulcer*

Date	Fasting Secretion: Volume	Fasting Secretion: Free Acidity	Maximum Free Acidity (Histamine)	Roentgen Examination	Gastroscopic Examination
4/ 2/36	..	..	..	Small gastric ulcer	
4/13	..	7 (Ewald)			
4/16	..	..	..	Shallow ulcer	
4/17	..	..	..	.....	Healing benign ulcer
5/27	..	..	..	Ulcer almost healed.....	Ulcer almost healed
6/17	..	..	..	.....	Healing ulcer
7/17	6	0	25	.....	Chronic ulcer
7/18	..	..	..	Ulcer 3 mm. in diameter	
10/23	..	..	..	Ulcer 1 cm. deep; 1 cm. wide	
10/28	..	..	..	.....	Ulcer still present
12/10	..	..	..	.....	Scar of healing ulcer
12/22	..	..	..	Ulcer 2 mm. deep; 2 mm. in diameter	
2/13/37	..	..	..	Ulcer healed	
3/17	..	..	..	.....	Very small ulcer
3/25	..	..	..	No ulcer	
4/14	..	..	..	.....	Small erosion at site of ulcer with scar formation
5/12	..	..	..	.....	Shallow ulcer still present
5/15	..	..	..	No ulcer	
6/23	..	..	..	No ulcer.....	Chronic healing ulcer
7/ 3	..	..	..	No active ulcer	
9/ 1	..	..	..	.....	Chronic ulcer 1 cm. in diameter
12/ 2	..	..	..	.....	Small shallow ulcer
1/ 5/38	..	..	..	.....	Ulcer not healed
1/10	..	..	..	No active ulcer	
1/12	12	0	50		
2/ 9	..	..	..	.....	Healed gastric ulcer
2/28	..	..	..	.....	Ulcer healed
3/10	..	..	..	.....	Scar only
3/15	..	..	..	No active ulcer	
3/29	..	..	..	.....	Scar only
7/ 6	..	..	..	.....	Recurrent ulcer 8 mm. in diameter
7/ 7	25	0	4		
7/11	35	0	55		
7/12	..	..	..	Recurrent ulcer; 14 mm. in diameter; 5 mm. in depth	
7/15	20	0	12		
7/21	28	0	20		
7/28	12	0	29		
8/ 2	..	..	..	Ulcer healed	
8/ 4	10	0	25		
8/ 5	..	..	..	.....	Recurrent ulcer
8/11	32	0	29		
8/18	22	0	45		
8/25	28	0	14		
8/26	..	..	..	.....	Shallow ulcer
9/ 8	20	0	26		
9/23	30	0	28		
10/ 6	5	0	20		
10/20	44	0	30		
11/ 7	42	0	50		
11/10	..	..	..	Ulcer 9 mm. in diameter	
11/19	..	..	..	.....	Ulcer smaller
12/ 1	14	0	0		
12/ 2	..	..	..	.....	Ulcer present
12/29	14	0	25		
1/ 6/39	..	..	..	.....	Ulcer almost healed
1/20	22	0	66	Ulcer healed	
1/27	..	..	..	.....	Ulcer healed
2/24	..	..	..	.....	Two ulcers at old site
3/10	25	0	17		
3/24	..	..	..	No active ulcer.....	Large crater
3/27	..	..	..	.....	Benign ulcer in old scar
3/30	10	0	30		
4/ 3	..	..	..	.....	Slightly more shallow
4/17	..	..	..	.....	Slightly smaller
5/20	35	0	34		
6/ 3	30	0	35		
6/23	3	..	..	.....	Large ulcer still present
7/ 5	..	..	..	No active ulcer	
7/14	..	..	..	.....	Ulcer about 15 mm. in diameter
9/20	75	0	41		

TABLE 2.—*Summary of a Study of a Patient with Gastric Ulcer—Continued*

Date	Fasting Secretion: Volume	Fasting Secretion: Free Acidity	Maximum Free Acidity (Histamine)	Roentgen Examination	Gastroscopic Examination
9/27	..	..	..	Small ulcer	
10/ 2	..	..	..	.....	Large benign ulcer
10/19	0	0	34		
10/20	..	..	..	Ulcer present	
10/23	..	..	..	.....	Huge benign ulcer about 15 mm. in diameter
11/ 3	..	..	..	.....	Large healing ulcer
11/10	5	0	26		
11/13	..	..	..	Marked decrease in size of ulcer	
11/22	18	0	4		
11/24	..	..	..	Very shallow ulcer	
11/25	14	0	0		
11/26	12	0	0		
11/27	4	0	0		
11/29	0	0	0		
12/ 1	0	0	0	.....	Ulcer healed
12/ 2	0	0	0		
12/ 5	..	..	..	Ulcer almost healed	
12/ 6	6	0	13	.....	Ulcer scar with converging fold
12/ 7	8	0	0		
12/13	11	0	0		
12/15	49	0	0		
12/18	57	13	35		
12/20	40	0	18		
12/22	40	0	26		
12/28	22	0	0		
1/ 4/40	23	0	0		
1/11	8	0	0	.....	Ulcer healed
1/25	26	0	10		
2/ 1	25	0	12		
2/ 8	15	0	4		
2/16	..	..	..	.....	Ulcer on old scar
2/23	21	12	35	.....	Ulcer healing
3/ 1	..	..	..	.....	Ulcer rather deep
3/ 7	31	0	32		
3/15	..	..	..	.....	Ulcer still present
3/18	..	..	..	Recurrent ulcer	
3/20	58	0	24		
3/29	..	..	..	.....	Ulcer still present
4/10	58	0	22		
4/12	..	..	..	.....	Very shallow ulcer
4/26	56	0	24		
4/29	..	..	..	Ulcer healed	
5/ 3	38	10	45		
5/17	..	..	..	.....	Benign ulcer
6/13	15	0	32		
6/21	..	..	..	.....	Rather small ulcer
7/15	..	..	..	.....	Ulcer not as deep
8/26	..	..	..	.....	Ulcer about 15 mm. in diameter
8/27	25	0	20	Healed gastric ulcer	
10/ 7	..	..	..	.....	No change
11/18	..	..	..	.....	Ulcer smaller
12/ 2	30	0	36		
1/ 6/41	..	..	..	.....	Ulcer healed or almost healed
1/20	26	11	31		
2/ 3	..	..	..	.....	Ulcer still visible
2/24	..	..	..	No active ulcer	
3/10	..	..	..	.....	Ulcer about 7 mm. in diameter
4/ 7	..	..	..	.....	Ulcer 5 or 6 mm. in diameter
4/21	70	5	32		
4/28	..	..	..	.....	No change
5/ 3	..	..	..	Scar but no active ulcer	
5/12	..	..	..	.....	No change
5/26	30	0	27		
6/ 2	..	..	..	.....	No change
6/30	..	..	..	.....	Ulcer about 3 mm. in diameter
7/21	31	0	0		
8/25	..	..	..	.....	Ulcer entirely healed
10/ 3	..	..	..	.....	Recurrent shallow ulcer
10/17	..	..	..	.....	Shallow ulcer 3 mm. in diameter
10/31	11	0	13		

The same remarks apply to an interesting case recently studied through the kindness of Dr. George F. Dick.

The patient, J. W., was a man aged 50 who entered Albert Merritt Billings Hospital with a history of intermittent epigastric distress of six years' duration. There was a definite history of syphilis, but repeated blood Wassermann and Kahn tests at the time of hospitalization were negative; the spinal fluid examination also gave negative results. Roentgen examination on Aug. 23, 1941, disclosed a probably benign penetrating ulcer of the lesser curvature (fig. 1). Gastroscopic examination by Dr. Schindler revealed an unusual ulcer of the lesser curvature of the stomach with no evidence of malignant change. The gastric analyses are given in table 3.

Subsequent roentgen examinations showed a marked decrease in the size of the ulcer and complete disappearance of the niche by September 25. The patient

Fig. 1.—Roentgenogram of penetrating ulcer of the lesser curvature of the stomach just below the cardia taken on Aug. 23, 1941.

died suddenly on October 2. Autopsy disclosed syphilitic aortitis with apparently complete occlusion of the left and marked narrowing of the right coronary ostium. The gastric ulcer was found to be completely healed (fig. 2). On histologic examination, no significant evidence of syphilis was found in the healed lesion, although the possibility could not be excluded completely.

Rodgers and Jones [21] described a type of acute or subacute small gastric ulcer, 2 to 5 mm. in diameter, not detected by roentgen examination and found by gastroscopic examination only in the presence of a "thin, atrophic mucosa and associated with absence or diminution in the secretion of acid." The ulcers were not seen at subsequent

21. Rodgers, H. W., and Jones, F. A.: Subacute Ulceration of Stomach Associated with Atrophy of the Gastric Mucosa and with Absence or Diminution in Secretion of Hydrochloric Acid, St. Barth. Hosp. Rec. **71**:140, 1938.

examinations two to four weeks later. Seventeen such cases were encountered in 600 gastroscopic examinations. One patient had pernicious anemia and a strongly positive Wassermann reaction. Seven of the 17 had histamine achlorhydria. Rodgers and Jones stated that they had never seen "large chronic gastric ulcers . . . in patients with a uniformly thin mucosa and either a low acid curve or achlorhydria." Schindler and I, in our combined studies, have not as yet seen such acute ulcer in patients with complete and persistent achlorhydria. In 4,277 examinations with the flexible gastroscope, Schindler [22] conducted 69 gastroscopies in 48 patients with pernicious anemia without encountering a single instance of the type described by Rodgers and

TABLE 3.—*Gastric Analyses of a Patient with Ulcer of the Lesser Curvature of the Stomach*

Date	Histamine, Mg.	Highest Acidity: Clinical Units (Titrated)	Highest Acidity: p_H (Beckman)
8/26/41	0.65	0	...
8/30	0.65	0	...
9/17	1.0*		
	0.5†	7	...
	0.5†	13	...
9/23	0.9	0	4.2
9/25	1.0	0	7.35
	0.5†	0	3.7
	0.5†	8	2.92
9/30	1.0	0	6.17
	0.5†	0	3.79
	0.5†	7	2.75

* The first histamine test on September 17 was excluded because fluoroscopic examination disclosed the tip of the tube to be in the duodenum at the ligament of Treitz. The figures given are for the second test performed when the tube was in the stomach. The position of the tube was not checked in the examinations of August 16 and 30. It was verified in the examination of September 23.

† Test made twenty minutes after the preceding test.

Jones. Gutzeit [23] reported finding, during one gastroscopic examination, acute ulcer in a patient with pernicious anemia and histamine-proved anacidity and without ulcer symptoms. The diagnosis was not confirmed by further gastroscopic or roentgen studies. The possibility exists that small acute ulcer may appear in the presence of persistent histamine achlorhydria. The occurrence cannot be considered, however, as completely proved. Large chronic ulcer apparently develops only in an acid-secreting stomach. The validity of this conclusion is further shown by the failure of Kahn [24] to find a single peptic ulcer in 840

22. Schindler, R.: Personal communication to the author.

23. Gutzeit, K.: Die Gastroscopie im Rahmen der klinischen Magendiagnostik, Berlin, Julius Springer, 1929.

24. Kahn, J. R.: Absence of Peptic Ulcer in Pernicious Anemia, Am. J. M. Sc. **194**:463, 1937.

cases of pernicious anemia and by the failure of Washburn and Rozendaal [25] to find an ulcer in 906 consecutive cases of pernicious anemia.

The experimental ulcer of Code, Varco and Wangensteen [14a] produced by prolonged gastric secretion resulting from the injection of histamine suspended in beeswax apparently has a clear clinical counterpart in the ulcer of Curling.[26] Necheles and Olson found experimentally that after extensive burns there is a "rapid and sustained increase in gastric secretion amounting to several hundred per cent."

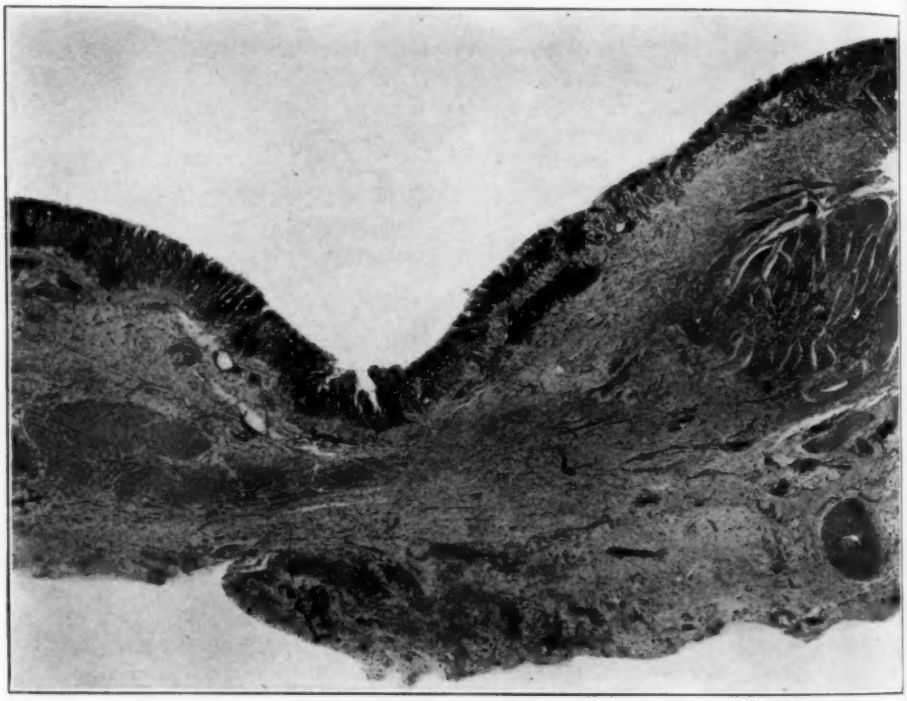

Fig. 2.—Photomicrograph (× 8) of healed gastric ulcer. Note the complete regeneration of the mucosa with complex tubular glands and the fusion of the muscularis mucosae with the muscularis propria in the scar tissue of the healed ulcer.

Code and Macdonald [27] found a marked rise in the histamine-like activity of the blood following burns. Rosenthal [28] found this histamine-

25. Washburn, R. N., and Rozendaal, H. M.: Gastric Lesions Associated with Pernicious Anemia, Ann. Int. Med. **11**:2172, 1937.

26. Harkins, H. N.: Acute Ulcer of the Duodenum (Curling's Ulcer) as a Complication of Burns: Relation to Sepsis, Surgery **3**:608, 1938.

27. Code, C. F., and Macdonald, A. D.: The Histamine-Like Activity of Blood, Lancet **2**:730 1937.

28. Rosenthal, S. R.: The Toxin of Burns, Ann. Surg. **107**:111 and 257, 1937.

like substance to differ from histamine in various respects such as heat lability. The evidence strongly suggests, however, that Curling's ulcer is a result of excessive gastric secretion induced by the presence in the blood of histamine or a histamine-like toxin produced by the burn.

It seems clear, then, in summary, that peptic ulcer results from a failure of the cells of the mucosa and of the wall of the stomach or the intestine to withstand the digestive action of acid gastric juice. The cause of the failure is not clear. Perhaps the secretion of protective mucus is insufficient. Perhaps the cellular resistance or cellular viability, whatever these terms may mean, is inadequate. In any event, the acid attack exceeds the capacity of the protective mechanism. Absolute hyperacidity need not be present, but merely a relative hyperacidity, as Büchner pointed out. It is relative in the sense that the hydrogen ion concentration and the proteolytic activity of the gastric juice exceed in destructive effect the defensive capacity of the cell. Tissue necrosis and digestion thus take place and lead to an erosion. Healing may occur, or the process may continue to the formation of acute ulcer. At any stage the lesion may heal, simply persist (becoming either subacute or chronic) or it may increase in size.[29] Regenerative activity is present at all times; whenever it becomes dominant, healing occurs.

MECHANISM OF PAIN

A comprehensive consideration of the mechanism of gastric pain, and specifically of the pain of peptic ulcer, is beyond the scope of this paper. Continued experience, however, has been in accord with the view expressed in 1926,[30] that acid gastric juice is primarily responsible not only for the development and the extension of the ulcer but also for the concomitant inflammation (a true chemical inflammation) and for the pain as well. Active inflamed ulcer, the inflammation resulting from the acid attack, is a sensitive lesion. The visceral nerves, ordinarily insensitive to such stimuli as cutting, pinching and tearing, become sensitive to both mechanical and chemical irritation. Carlson and other workers,[31] using the balloon and kymograph method, showed that under such circumstances, the pain threshold is crossed by the mechanical stimuli arising from peristalsis. In 1 patient studied during

29. Palmer, W. L.; Schindler, R., and Templeton, F. E.: Development and Healing of Gastric Ulcer: A Clinical, Gastroscopic and Roentgenologic Study, Am. J. Digest. Dis. **5**:501, 1938.

30. (*a*) Palmer, W. L.: The Production of Pain by Means of Chemical Irritants, Arch. Int. Med. **38**:694 (Dec.) 1926; (*b*) The Pain of Gastric Carcinoma, ibid. **39**:126 (Jan.) 1927. (*c*) Palmer, W. L., and Heinz, T. E.: Further Observations on the Mechanism of Pain in Gastric and Duodenal Ulcer, ibid. **53**:269 (Feb.) 1934.

31. Palmer, W. L.: Role of Peristalsis and Spasm, Arch. Int. Med. **39**:109 (Jan.) 1927.

operation under local anesthesia, Dragstedt and Palmer [32] found the ulcer exceedingly sensitive to the slight trauma of lightly stroking the serosal surface. Pinching and circular spasm of the muscle in the region of the ulcer evoked severe pain. The flow of acid on the surface of the ulcer likewise evoked pain. Palmer [30a] had previously shown that the injection of acid gastric juice or of a solution of hydrochloric acid into the stomach is sufficient to evoke pain in a peptic ulcer, provided the pain mechanism is sensitive at the time of the injection. The manner in which the pain threshold may be traversed by the action of acid is illustrated in the following episode:

A man 49 years of age who had suffered with recurring duodenal ulcer for nearly twenty years was admitted to the hospital for treatment. His pain was severe. Roentgen examination disclosed a large crater in the duodenum. Toward the end of a histamine test revealing a free acidity ranging from 90 to 100 clinical units, such severe pain developed that the patient doubled up in bed. Four grams of sodium bicarbonate dissolved in 100 cc. of water were allowed to run into the stomach through the tube. Complete and spectacular relief occurred within two to three minutes, according to the intern's note. In time, after ulcer management, the pain-producing mechanism of the lesion became desensitized; this was evidenced by the fact that all spontaneous pain disappeared, and repeated histamine tests were carried out without pain. No other acid tests were made.

In another patient, a man 43 years of age, severe continuous pain radiating through to the back apparently required frequent injections of morphine for relief. With the demonstration of a duodenal crater and a histamine-free acidity of 108 clinical units, the patient was submitted to a program of acid neutralization with spectacular relief from the pain. Subsequently, an acid test was carried out; 200 cc. of a 0.5 per cent solution of hydrochloric acid was injected into the empty stomach. Typical pain developed in the back and progressively increased in severity during the course of twenty minutes. The pain was said by the patient to have been exactly like that experienced in his previous most severe attacks. The injection of 4.0 Gm. of sodium bicarbonate in 60 cc. of water was followed by gradual subsidence of the pain; complete relief was obtained in twenty to thirty minutes. With continued antacid ulcer management the spontaneous pain ceased entirely; the ulcer crater disappeared in the roentgenograms, and at the end of six weeks, the patient was able to tolerate three separate injections at thirty minute intervals of 200 cc. each of 0.5 per cent solution of hydrochloric acid with no distress whatsoever during the ninety minutes of the test.

As noted previously, this desensitization of the pain mechanism followed treatment designed to protect the ulcer from the corrosive action of the gastric juice and coincided with roentgen evidence of progressive healing. The dominant role of acid gastric juice in the entire process thus seems apparent.

With regard to the precise mechanism of the production of pain, it seems clear that the first essential is a lowering of the pain threshold of the nerve endings, presumably as a result of inflammation. The pain derived from mechanical irritation is apparently a pressure phenomenon.

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32. Dragstedt, L. R., and Palmer, W. L.: Direct Observation on the Mechanism of Pain in Duodenal Ulcer, Proc. Soc. Exper. Biol. & Med. **29**:753, 1932.

The pain induced by the acid is, in all probability, due to the direct irritation of the nerve endings by the acid solution. Moore and associates [33] found that solutions as weakly acid as p_H 6.0 produced stimulation of the nerve endings in blood vessels and capillary loops. Solutions as slightly alkaline as p_H 9.2 produced similar effects. In a peptic ulcer, nerve endings are exposed to solutions whose p_H is between 1 and 2 for several hours of every day. The puzzle, it would seem, is not the appearance of pain, but rather the absence of pain in certain cases. These may be rather insensitive persons with high pain thresholds in whom the digestive action of the gastric juice succeeds in destroying tissue but does not succeed in producing sufficient inflammation to lower the pain threshold to the point necessary for the production of pain.

THE HEALING OF PEPTIC ULCER

All ulcers may and the majority do heal in spite of the presence of acid gastric juice. This is evidenced by the spontaneous remissions so characteristic of the disease and by the healed lesions encountered in routine autopsy work. In all ulcers, regenerative processes begin early and continue until the tissue is destroyed or healing occurs. Apparently the balance of these tissue-regenerating and tissue-digesting processes is a delicate one, easily tipped one way or the other, and leading either to healing or to extension of the ulcer. Whether or not the remissions, the healing and the recurrences are related, wholly or partially, to variations in gastric secretion is not known. From the evidence offered of the role of acid digestion in the pathogenesis of ulcer, one would expect a priori that healing would occur more rapidly and more surely when the lesion is protected from the action of acid gastric juice. Daily clinical experience supports this concept. Some years ago an attempt was made to obtain more definite objective evidence on this point by subjecting two comparable groups of hospitalized patients to programs of therapy which differed only in that alkali was administered to one group in large amounts, while beef extract was given the other group as a substitute for the alkali. The design was to neutralize the gastric acidity in the group given alkali and to stimulate acid secretion in the group given beef tea.[34] The diet was the same for both groups. The rates of disappearance of spontaneous pain and of desensitization to the acid test were used as criteria of rates of healing, since subsidence of the inflammatory reaction is presumably the first step in the healing process. The average duration of spontaneous pain was two and eight-tenths days for those given alkali and

33. Moore, R. M.; Moore, R. E., and Singleton, A. O.: Experiments on the Chemical Stimulation of Pain-Endings Associated with Small Blood Vessels, Am. J. Physiol. **107**:594, 1934.

34. Palmer, W. L.: The Value of Acid Neutralization in the Treatment of Gastric and Duodenal Ulcers, Arch. Int. Med. **46**:165 (Aug.) 1930.

twenty-six and six-tenths days for those given beef tea. The average duration of sensitivity to the acid test was nine and seven-tenths days for those given alkali and twenty-six and nine-tenths days for those given beef tea. It thus seems clear that the neutralization of the acid facilitated the process of healing.

There is a great deal of direct and indirect evidence that the problem of ulcer therapy would be solved if there were available a safe and suitable method of producing complete and permanent achlorhydria. There is none, that is, none short of total gastrectomy. Conversely, the continued secretion of abundant highly acid gastric juice constitutes the greatest hindrance to healing. Such secretion not infrequently occurs with or without stenosis and obstruction, either spastic or cicatricial. Gastric ulcer is frequently accompanied by pylorospasm, benign hypertrophy of the pylorus, antral spasm or, indeed, by active or healed intrapyloric ulcer with resultant delay in gastric emptying and prolongation of the period in which the ulcer-bearing surfaces of the stomach and the duodenum are bathed in acid gastric juice. The case summarized in considerable detail on page 9, however, constitutes an exception in that gastric secretion was low and no evidence of a delay in gastric emptying was observed at any time. It is tempting to ascribe the poor healing and frequent recurrences seen in this instance to a poor *vis conservatrix* or *formativa,* for the patient seemed to have little *vis vitalis!* The fact that marked differences do occur in the healing capacities of the tissues in different persons is well known, but the underlying causes are obscure.

METHODS OF PROMOTING HEALING OF PEPTIC ULCER

The most effective means of promoting healing is to prevent the ulcer from coming into contact with acid gastric juice. Duodenal ulcer treated by Finsterer's *resectio ad exclusionem* invariably heals. Duodenal ulcer heals regularly after gastroenterostomy, presumably because this procedure provides sufficient diversion of the pyloric stream. Gastroduodenostomy likewise is followed by disappearance of the initial lesion. Pyloroplasty, as might be expected, does not give such uniform results. The chief difficulty with these various surgical therapeutic procedures, including subtotal gastrectomy, is not that they fail to lead to the healing of the primary ulcer but rather that new ulcers form at the new stomas.

Medical methods for promoting the healing of a given lesion are less certain and less spectacular. The oldest procedures (so old that their origin is shrouded in the clouds of antiquity) are rest and a milk diet. Little is known about the effects of exercise and rest on the digestive process, but there is some evidence that exercise increases gastric secretion. The effect of worry and nervous strain on secretion and on gastric emptying likewise needs further elucidation. With regard

to the milk diet, however, definite information is available, for milk is one of the best neutralizers of acid gastric juice; for example, 10 cc. can neutralize 11 cc. of 0.3 per cent hydrochloric acid.[35] All protein foods have definite neutralizing value. This capacity is utilized consciously or unconsciously in the various frequent feeding programs. The origin of the use of alkali in the treatment of peptic ulcer, like that of rest and a milk diet, is so old that its source is unknown. Sippy was the first to develop a comprehensive program of acid neutralization based on the use of food and alkali. A complete discussion of the details of management is beyond the scope of this paper.[36]

The inhibition of gastric secretion is difficult to accomplish. Atropine does diminish the volume and, if given in therapeutically impossible dosage, ultimately the free acidity also.[37] It inhibits gastric emptying. Figure 3, provided by my associate, Dr. Alfred J. Klein, illustrates the manner in which 1.0 mg. of atropine injected subcutaneously prior to feeding inhibits the immediate postfeeding secretion of a modified Heidenhain pouch in the dog. The prolongation of the period of secretion is noteworthy. Presumably this is due to two factors: (1) escape from the effect of atropine and (2) delayed gastric emptying with a rise in pouch secretion as the stomach resumes emptying. Atropine given after the meal is rather less effective, but the same general action may be seen. The effect observed is primarily on the volume of the secretion rather than the acidity, as other workers have noted, for the acidity of the pouch secretion ranges from 120 to 160 unless the volume becomes markedly depressed; when this happens, the acidity also drops.

Various extracts capable of depressing gastric secretion and resembling enterogastrone[38] have been obtained from urine, but none

35. Freezer, C. R. E.; Gibson, C. S., and Matthews, E.: A Contribution to the Study of Alkalis as Therapeutic Agents, Guy's Hosp. Rep. **78**:191, 1928.

36. Kirsner, J. B., and Palmer, W. L.: The Effect of Various Antacids on the Hydrogen-Ion Concentration of the Gastric Contents, Am. J. Digest. Dis. **7**:85, 1940. Palmer, W. L.: Diseases of the Stomach, in Barr, D. P.: Modern Medical Therapy in General Practice, Baltimore, Williams & Wilkins Company, 1940, vol. 2, pp. 2261-2286; Peptic Ulcer, in Portis, S. A.: Diseases of the Digestive System, Philadelphia, Lea & Febiger, 1941, pp. 513-533; Diseases of the Stomach, in Cecil, R. L.: A Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1940, pp. 776-792. Freezer, Gibson and Matthews.[35]

37. Porter, R. T.: Studies on the Effect of Atropine on Gastric Secretion, Proc. Soc. Exper. Biol. & Med. **29**:504, 1932.

38. Culmer, C.; Atkinson, A. J., and Ivy, A. C.: Depression of Gastric Secretion by the Anterior Pituitary-Like Fraction of Pregnancy Urine, Endocrinology **24**:631, 1939. Gray, J. S.: Present Status of Urogastrone, Am. J. Digest. Dis. **8**:365, 1941. Friedman, M. H. F., and Sandweiss, D. J.: The Gastric Secretory Depressant in Urine, ibid. **8**:366, 1941. Gray, J. S.; Bradley, W. B., and Ivy, A. C.: On Preparation and Biological Assay of Enterogastrone, Am. J. Physiol. **118**:463, 1937. Quigley, J. P.: Enterogastrone: Significant Steps in the Development of Present Conceptions, Am. J. Digest. Dis. **8**:363, 1941.

of these substances has as yet been widely available for clinical study. Metz and Lackey [39] were led to use posterior pituitary in the treatment of peptic ulcer by noting polyuria associated with the ulcer syndrome. The patients received 40 mg. four times daily by nasal insufflation. "The excellent results obtained in this series were striking." I have had no clinical experience with this method, but Dr. Klein has made some interesting experimental observations. Figure 4 shows the marked

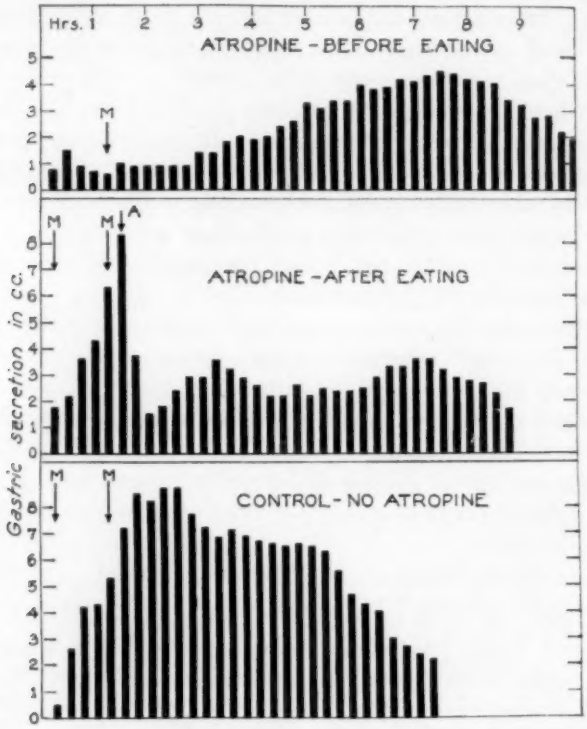

Fig. 3.—The effect of atropine on the volume of gastric secretion of a dog with a Heidenhain pouch. The bars represent cubic centimeters of secretion in fifteen minute periods. *M* indicates the feeding of a 100 Gm. bolus of meat. In the top section (average of six experiments in 3 dogs) 1 mg. of atropine was injected subcutaneously before the feeding; in the middle section (average of seven experiments in 3 dogs) the atropine was injected following a double meal; the control studies (average of seven experiments in 4 dogs) are shown in the bottom section.

and prolonged inhibition of gastric secretion in a dog with a modified Heidenhain pouch induced by the intramuscular injection of 2 cc. of

39. Metz, M. H., and Lackey, R. W.: Peptic Ulcer Treated by Posterior Pituitary Extract, Texas State J. Med. **34**:214, 1938.

solution of posterior pituitary. In figure 5 a similar although less spectacular effect may be noted from the intranasal insufflation of posterior pituitary in the form of powder. Klein and Schindler observed gastroscopically that the gastric mucosa of the dog during the period of this effect changes from orange red to snow white, indicating presumably intense vasoconstriction.

Intensive radiation therapy results in a variable depression of gastric secretion lasting a variable time. In 88 patients treated by Palmer and

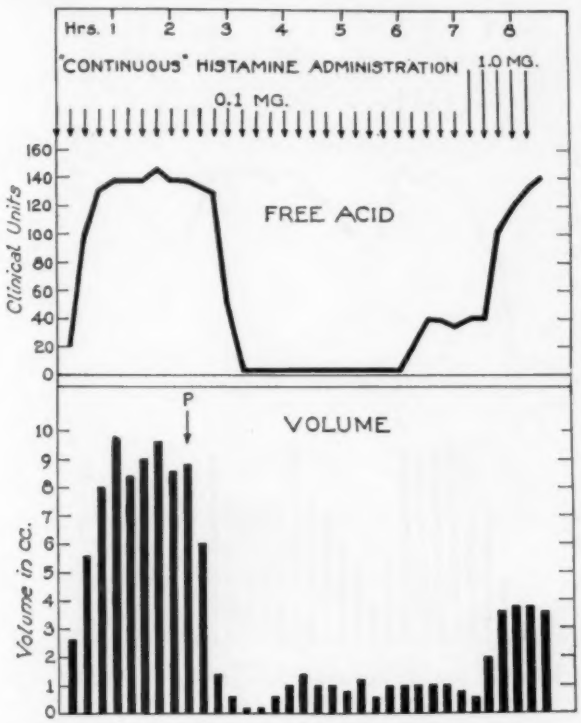

Fig. 4.—The effect of surgical pituitrin on the gastric secretion of a dog with a Heidenhain pouch. The profuse highly acid secretion induced by the subcutaneous injection at fifteen minute intervals of 0.1 mg. of histamine biphosphate is abruptly inhibited by the subcutaneous injection of 2 cc. of surgical pituitrin at *P*.

Templeton,[40] complete histamine achlorhydria developed in 35 and persisted for periods of a few days to a few months. During the phase of achlorhydria symptoms of ulcer were invariably absent, and healing progressed. Failure of the ulcer to heal and recurrence of the ulcer occurred only in those cases in which achlorhydria did not develop or after the phase of achlorhydria had passed.

40. Palmer, W. L., and Templeton, F. E.: The Effect of Radiation Therapy on Gastric Secretion, J. A. M. A. **112**:1429 (April 15) 1939.

Figure 6 illustrates the various effects noted.

One patient received 3,600 r, and yet the depression as measured by the maximum free acidity following histamine was relatively slight and transitory. This patient, a man of 56, entered the hospital with an ulcer of only three years' duration but with roentgen evidence of a duodenal ulcer with an enormous crater and with moderate stenosis. At the time of writing, the patient has followed an antacid ulcer regimen meticulously for the past three and a half years. The crater disappeared within a few weeks and has not recurred, nor has the stenosis increased. There has been no return of symptoms. Of the rather large group

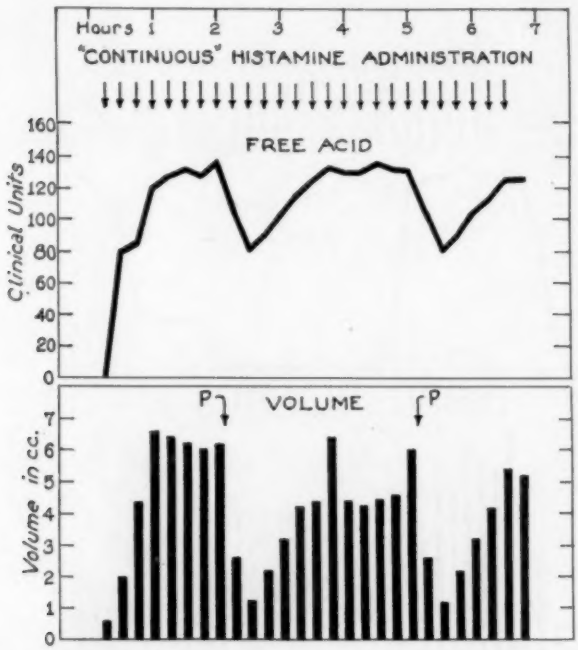

Fig. 5.—The effect on gastric secretion of the intranasal insufflation of posterior pituitary powder. The abundant continuous secretion of a dog with a Heidenhain pouch resulting from the subcutaneous injection of 0.1 mg. of histamine biphosphate every fifteen minutes is definitely, although incompletely, inhibited by the intranasal insufflation of 40 mg. of posterior pituitary powder (U. S. P. XI).

subjected to roentgen therapy, this patient was one of those whose gastric secretion was least affected.

A more typical response is that exhibited by the first patient treated by Templeton and me. The patient, a man 35 years of age, was seen in 1930 with stenosing duodenal ulcer of indefinite duration. Gastroenterostomy was performed in 1933 and undone in 1936 because of recurrent jejunal ulcer. The duodenal ulcer recurred, and in April 1937, the patient was given 2,930 r of therapy; after this complete achlorhydria to histamine developed and persisted from the twenty-seventh to the hundred and thirteenth day, returning to approximately normal by the two hundred and thirty-seventh day. The patient was advised to resume

his antacid program with the return of normal acidity but did so only to a limited extent. Moderate symptoms have recurred occasionally, and at times there has been roentgen evidence of a small crater in the duodenum, although the differentiation in this case between scar and crater has proved difficult.

In another case occurred the most prolonged depression observed. The patient, a man 38 years of age, entered the hospital with a history of ulcer of eight years' duration and a crater on the lesser curvature of the stomach about 1 cm. in diameter as seen roentgenologically. With medical management the symptoms were promptly relieved, and the crater disappeared. Roentgen therapy (2,937 r given in June 1937) resulted in complete achlorhydria to histamine appearing on the ninety-sixth day. As may be seen from figure 6, this persisted until the four

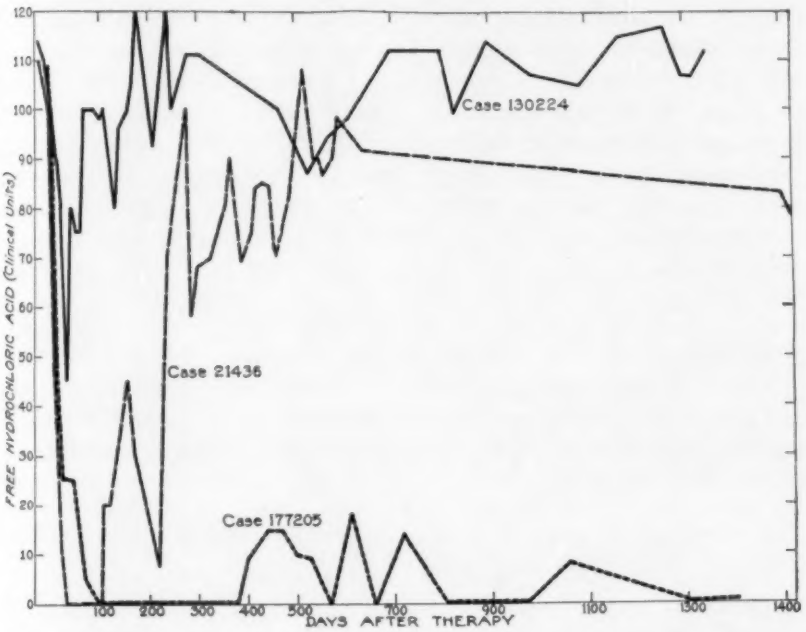

Fig. 6.—The depression of gastric acidity by roentgen therapy. Three cases illustrating the varying results obtained. The curves are based on the maximum free acidity present in individual histamine tests (see text).

hundred and fourth day. The gastric secretion at the end of four years was still extremely low. There have been no digestive symptoms of any kind. Roentgen and gastric studies have disclosed no evidence of ulcer. For the past three years the patient has eaten a general diet.

INDICATIONS FOR MEDICAL TREATMENT

Active medical treatment is indicated in all cases of active peptic ulcer. When healed lesions are encountered, judgment as to the dietary and other restrictions to be advised, if any, must be based on the duration of the remission and the various other factors present.

INDICATIONS FOR OPERATION

The indications for operation arise, in essence, from the complications of ulcer, the most urgent, of course, being acute perforation. Subacute and chronic perforations do not necessarily constitute indications. Massive hemorrhage is best treated medically at the time of hemorrhage, although in selected cases surgical attempts to tie off the bleeding artery or even to excise the lesion may properly be elected. In certain instances of recurring massive hemorrhage subtotal gastric resection in an interval between episodes of bleeding may be desirable. However, even subtotal gastrectomy does not guarantee against recurrent massive hemorrhage.[41] The most frequent indication for operative treatment is stenosis. In my experience even stenosis does not necessarily require operation unless the stenotic lumen is reduced to a diameter of only 3 mm. or less as judged by fluoroscopic study. Gastric ulcer should be removed if there is serious question as to whether it is benign or malignant; this is of course the question unless it heals satisfactorily within reasonable time under medical treatment. Healing should be judged not from disappearance of symptoms but from objective roentgen and gastroscopic disappearance of the crater. Jejunal ulcer may be treated medically, although as a rule its management is more difficult than is that of primary gastric or duodenal ulcer, and hence operation may be in order. In the final analysis, it must be recognized that no medical or surgical procedure, except total gastrectomy, will regularly result in complete and permanent achlorhydria and that hence there is no method of therapy which regularly results in the complete and permanent cure of the disease peptic ulcer.

41. Kirsner, J. B., and Palmer, W. L.: The Treatment of Massive Hemorrhage from Peptic Ulcer, Internat. Clin. **4**:105, 1939.

GASTROSCOPIC DIFFERENTIAL DIAGNOSIS OF BENIGN AND MALIGNANT ULCER OF THE STOMACH

AN ANALYSIS OF THE GASTROSCOPIC PICTURE OF ONE HUNDRED AND THIRTY-THREE LESIONS

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Because gastroscopy is a minor procedure that can be performed in the office and is carried out with no real discomfort to the patient when the proper technic is used, the gastroscopic method has been widely accepted within the last few years. Its value in the diagnosis of chronic gastroduodenal ulcer has been discussed thoroughly and repeatedly.[1] Therefore, only a brief summary of the chief facts will be given here.

Roentgen examination is superior to gastroscopy in the diagnosis of chronic gastroduodenal ulcer. The duodenal ulcer cannot be seen with the gastroscope. Benign ulcer of the pyloric ring cannot be seen with a gastroscope because the pylorus is drawn out of the visual field by adhesions. Some benign gastric ulcers of the lesser curvature of the antrum and of that small stripe of the posterior wall on which the gastroscope is lying escape detection with the gastroscopic method. Most gastric ulcers are seen clearly through a gastroscope, and there is a small but not unimportant group of gastric ulcers which escape even the most refined roentgen relief compression technic but which can readily be seen with a gastroscope. The healing process of benign gastric ulcer is best observed by a gastroscope. The condition of the mucosa surrounding the ulcer and at a distance from the ulcer can be determined only by gastroscopic observation.

The most important statement, however, about the usefulness of gastroscopy in cases of gastric ulcer is that gastroscopy is the best method for the differentiation of benign and malignant ulcer.

From the Department of Medicine, the University of Chicago.

1. Schindler, R.: (*a*) Gastroscopy, the Endoscopic Study of Gastric Pathology, Chicago, The University of Chicago Press, 1937; (*b*) The Value of Gastroscopy in Diagnosis and Surgical Treatment of Chronic Gastroduodenal Ulcer, Surgery **2**:692, 1937.

It is the purpose of this paper to amplify and prove this statement by the analysis of the gastroscopic picture of 133 gastric ulcers in which the differential diagnosis had to be considered.

This differential diagnosis is considered to be difficult and often impossible. However, Palmer [2] came to the conclusion that "although there is no pathognomonic sign to indicate the benign nature of a lesion, the total evidence available from careful study permits the clinical differentiation of benign and malignant gastric ulcer with a high degree of accuracy." He came to this conclusion from clinical, roentgen and gastroscopic experience. As long as the opinion was prevalent that chronic gastric ulcer often undergoes carcinomatous transformation, the exact differential diagnosis was not so important from a practical viewpoint. Now more and more the conviction gains ground that benign ulcer rarely if ever precedes gastric carcinoma and that the two diseases are separate entities.[3] If this is so, then the differential diagnosis becomes of the greatest practical importance. Delaying operation on resectable carcinoma by the so-called therapeutic test is hardly justified because in the waiting time the tumor may become inoperable. The resection of every benign ulcer is still less justified, as most ulcers can be treated medically. Resection has a definite mortality rate, and even the end results of such an operation are not always satisfactory.[4] Every method, therefore, which permits improvement of the differentiation between these two lesions needs thorough consideration.

The facts that gastroscopy is superior in making the differential diagnosis between benign and malignant ulcer even to the inspection of the gross specimen and that it is equaled only by microscopic examination have been explained by the blood circulating in the living tissue which makes the gastroscopic picture plastic. Detailed discussion of this question has been given elsewhere.[3] However, it was to be expected that gastroscopy, like any other diagnostic method, would not be infallible, and this expectation has been fulfilled. Gastroscopy is in a period of development, and every new experience adds new diagnostic criteria.

The important relation between the results of the gastroscopic and the roentgen method will not be discussed. This material is being collected by our roentgenologic collaborator, Dr. Frederic Templeton, and will be extensively presented by him. It may be mentioned that by

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2. Palmer, W. L.: Benign and Malignant Ulcers: Their Relation and Clinical Differentiation, Ann. Int. Med. **13**:317, 1939.

3. Schindler, R.: Early Diagnosis of Cancer of the Stomach; Gastroscopy and Gastric Biopsy; Gastrophotography and X-Rays, J. Nat. Cancer Inst. **1**:451, 1941.

4. Schindler, R.: Gastroscopic Observations in Resected Stomach, Am. J. Digest. Dis. **7**:502, 1940.

roentgen examination the number of localized lesions seen is greater than that seen by gastroscopy. By gastroscopy 24 lesions were missed; but by roentgen examination only 16 lesions were overlooked. The number of wrong differential diagnoses is about the same with each method. By gastroscopy 6 lesions were wrongly diagnosed; by roentgen examination 9 wrong differential diagnoses were made. The chief difference, however, is in the number of indefinite diagnoses among the 113 gastric ulcers seen by gastroscopy. A noncommittal indefinite diagnosis was made in only 2 cases; but at roentgen examination in 15 cases no commitment was made. All these figures refer only to the first examination. Frequently, if there was nonagreement between the results of roentgen examination and of gastroscopy, the patient was reexamined by both methods, and the results obtained with the one method sometimes influenced the interpretation of the findings obtained by the other method decisively.

Although the results of gastroscopy were rather satisfactory in our series, we asked ourselves whether these cases could teach us a better evaluation of the picture observed at the gastroscopic examination and whether the number of wrong or indefinite gastroscopic differential diagnoses could still be reduced. This analysis concerned 113 gastric ulcers visualized gastroscopically, 79 of which proved to be benign ulcers, and 34, malignant. The final diagnosis was established in every case, either from the patient's recovery after medical treatment as proved by clinical observation and roentgen or gastroscopic reexamination or from microscopic sections after operation or autopsy. We tried to answer the following questions: 1. Which gastroscopic signs speak in favor of benign ulcer? 2. Which gastroscopic signs are not proof of benign ulcer? 3. Which gastroscopic signs speak in favor of malignant ulceration? 4. Which gastroscopic signs are not proof of malignant ulceration?

It is not within the scope of this paper to describe extensively the gastroscopic aspect of the normal or the pathologic gastric mucosa or to describe the common pictures of benign and malignant gastric ulcer. Such discussion will be found elsewhere.[1a]

SIGNS IN FAVOR OF BENIGN ULCER

Perfectly Sharp Edge Without a Surrounding Wall.—Since in the gastroscopic picture, in contrast to the picture obtained in the gross specimen, the ulcer floor is a different color from that of the surrounding gastric mucosa, it usually is easy to state whether or not the edge of the ulceration is sharp and punched out or not. This sharpness of the edge must not be confused with a regular edge; as will be shown later, the edge of an ulcer can be irregular and still have a sharply cutout

appearance. In 72 of 79 cases of benign ulcer, the gastroscopic picture showed a punched-out lesion with perfectly sharp edges and no surrounding wall. All of these ulcers with the exception of 5 were located in the body of the stomach, and most of them in or near the lesser curvature above the angulus.[5] Only 1 malignant ulcer in 34 cases had sharp edges, and this ulcer was located in the anterior wall of the antrum, close to the greater curvature. This case will be discussed separately. In some cases the huge wall of a tumor overlapped the edges of the ulcer so

Fig. 1.—Gastroscopic views of a benign and a malignant ulcer: *A*, benign ulcer. In the background the closing pylorus is seen. The parabolic curve is the angulus. Immediately above the angulus, an ulcer is seen. Its sharp, punched-out margin and the smooth noninfiltrated adjacent mucosa are characteristic of benign ulcer. *B*, malignant ulcer. A portion of the angulus is seen at the right side of the picture. The ulcer seen above in the lesser curvature cannot possibly be benign because of the unsharp blending edge and the stiff nodular infiltration of the surrounding tissue.

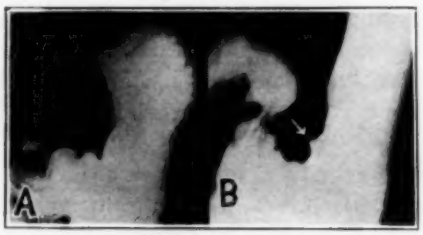

Fig. 2.—Roentgenograms of the 2 ulcers shown in figure 1. *A*, benign ulcer. Note the distance of the ulcer from the incisura angularis, which obviously is not identical with the angulus. *B*, malignant ulcer. A certain differential diagnosis from roentgen examination is not possible, although when observed gastroscopically, the difference between these 2 lesions is striking.

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5. The terminology of the portions of the stomach follows the suggestions given in the textbooks of gastroscopy (Schindler, R.: Lehrbuch und Atlas der Gastroskopie, Munich, J. F. Lehmann, 1923; footnote 1 *a*). Gastroscopically, the stomach is definitely divided into two cavities, the body and the antrum; the musculus sphincter antri forms the dividing line between them. The angulus, which is located at the same level as the musculus sphincter antri, constitutes the bend of the lesser curvature from a caudad to a cephalad direction. It does not necessarily correspond with the incisura angularis of the roentgenologist (fig. 2).

much that their character could not be determined. But the nature of the wall in these cases made the diagnosis of malignant ulcer certain. Therefore, it might be said that the sharp edge of an ulcer is one of the best gastroscopic signs of benignity.

No Infiltration of the Mucosa Whatever.—Only in benign lesions did we see an entirely normal and noninfiltrated mucosa encircling a sharply limited punched-out ulceration. Such a normal mucosa was found in 26 out of 79 benign ulcers. This statement probably will surprise those familiar with the European studies concerning gastritis combined with gastric ulcer. It has been contended [6] that inflammation is present in every case of gastric ulcer. However, gastroscopists have contended for a long time that this conception is wrong and that material obtained at operation contained artificial changes which had been misinterpreted.[7] Baxmeier and one of us (R. S.)[8] found that in ulcer-bearing stomachs inflammation was absent at all gastroscopic examinations in 47 per cent. The percentage obtained in the series presented in this paper is about 33 per cent. It is obvious that in contrast to Konjetzny's [6] conceptions no inflammation will be found grossly in a rather high percentage of all benign ulcers. The lack of inflammation around the ulcer often will be decisive for the differential diagnosis. In a 57 year old physician, a huge ulcer crater had been found on roentgen examination immediately below the cardia and had been interpreted as probable carcinoma; but on gastroscopic examination the sharp edges and the perfectly normal gastric mucosa around the ulcer spoke in favor of a benign lesion. Therefore, medical treatment was advised. The niche disappeared, the patient recovered and at the time of writing is still alive two and one-half years after the gastroscopic examination.

Hemorrhages and Pigment Spots Lying in a Normal Mucosa Localized Gastric Purpura.—In the paper published by Baxmeier and one of us (R. S.), it was stated that mucosal hemorrhages and pigment spots in a normal mucosa are found much more frequently in patients with ulcer-bearing stomachs than in other patients with abdominal distress. The relation of these lesions to gastric ulcer has been described elsewhere.[9] In our series we found them with 15 of 79 benign ulcers and with only 1 of 34 malignant ulcers. Therefore, their presence suggests

6. Konjetzny, G. E.: Die entzündliche Grundlage der typischen Geschwürsbildung im Magen und Duodenum, Berlin, Julius Springer, 1930.

7. Schindler, R.; Necheles, H., and Gold, R.: Surgical Gastritis: A Study on the Genesis of Gastritis Found in Resected Stomachs with Particular Reference to the So-Called "Antral Gastritis," Associated with Ulcer, Surg., Gynec. & Obst. **69**:281, 1939.

8. Schindler, R., and Baxmeier, R.: Mucosal Changes Accompanying Gastric Ulcer, Ann. Int. Med. **13**:693, 1939.

9. Schindler, R.: Chronic Localized Gastric Purpura, Am. J. Digest. Dis. **5**:796, 1939.

the benignity of an accompanying ulceration. This, however, is true only for the expert in gastroscopy. Mucosal hemorrhages lying in an inflamed mucosa are frequent in all types of inflammation and in our opinion have nothing to do with the lesions described as localized gastric purpura and with the formation of benign ulcer. The presence of hemorrhages and pigment spots can be used in favor of the diagnosis of benign ulcer only if the normal character of the mucosa in which they are lying is beyond any doubt. Of the 22 cases of benign ulcer visualized by roentgen examination but not seen gastroscopically, mucosal hemorrhages and pigment spots were seen in 4. Thus these lesions may be used as an indirect gastroscopic sign in favor of the benign nature of an ulcer seen only on roentgen examination.

Henning's Sign (Arch-Shaped Distortion of the Angulus).—The sign first described by Henning[10] is usually produced by an ulcer immediately behind the angulus lying in the blind area of the lesser curvature of the antrum which causes the otherwise smoothly rounded angulus to look like a Gothic arch. In the true Henning sign the angulus shows no sign of ulceration or inflammatory infiltration. But it may be present in cases in which the ulcer lies proximal to the angulus also. This sign was present in 4 of the 79 benign ulcers, but it was not seen in the malignant ulcerations. It appears that in cases in which a niche demonstrated by roentgen examination remains invisible gastroscopically behind the angulus, the presence of the Henning sign speaks in favor of the benignity of the ulcer. The irregularity of the angulus produced by malignant infiltration can and must not be confused with the true Henning sign. The experienced gastroscopist, furthermore, will remember that sometimes crossing folds may simulate an arch-shaped appearance of the angulus and that this has no diagnostic significance whatever.

Hourglass Fold.—In cases of true organic hourglass stomach, which are rare, a fold of the greater curvature protrudes deeply into the cavity of the stomach. In some cases it is possible to direct the tip of the gastroscope into the lower bag of the hourglass, and then if the instrument is withdrawn, the large fold will become visible, crossing the greater curvature from the anterior to the posterior wall. Sometimes the fold crosses the anterior wall up to the location of the ulcer in the lesser curvature. This unmistakable picture, which we observed in 3 cases of benign ulcer, was not found in any case of malignant lesion. In the cases of malignant hourglass stomach we have seen, we were not able to pass the instrument into the lower bag.

10. Henning, N.: Die Entzündung des Magens, Leipzig, Johann Ambrosius Barth, 1934.

Converging Folds.—Converging folds are seen less frequently by gastroscopic than by roentgen examination,[11] especially when the ulcer is healing; and it seems that the folds observed only by roentgen examination have their origin in the scarring of the lower layers of the gastric wall. However, they are seen by gastroscopy also, radiating toward the margin of the ulcer. They were found to be present in 16 of 79 benign ulcers. Only in 1 malignant ulcer was a single fold seen to cross the anterior wall toward the margin of the ulcer, which was surrounded by an extremely high edematous wall. This case will be described in detail later.

SIGNS WHICH ARE NOT PROOF OF BENIGN ULCER

Normal Mucosa Distant from the Ulcer.—As we said before, sometimes there is no inflammation present with benign ulcer. According to the European literature [12] one would think that this would never occur with malignant ulcer, because there is almost unanimity that gastric carcinoma develops in a gastritic, usually atrophic, mucosa. This may be true for the mucosa immediately surrounding malignant ulcer, but in 5 of 34 malignant ulcers, perfectly normal mucosa was found distant from the lesion. An apparently normal mucosa may therefore be found in both malignant and benign ulcers and cannot be used for the differential diagnosis.

Uniform Color of the Wall and the Surrounding Mucosa.—As will be shown later, the contrast of the color of the wall and the surrounding mucosa is diagnostic for carcinoma. However, in 9 of 34 malignant ulcers, the wall surrounding the ulcer was the same orange red color as the surrounding mucosa, so that uniform color of the wall and the mucosa is no proof of the benign nature of a lesion.

Mucosal Islands Within the Ulcer.—Mucosal islands growing within the ulcer floor were seen in 3 of the 79 benign ulcers and in 1 of the 34 malignant ulcers. They cannot be used in favor of either diagnosis.

SIGNS WHICH SPEAK IN FAVOR OF MALIGNANT ULCER

Limiting Wall on One Side and Blending Infiltration on the Other Side.—If there is a blending of the color of the ulcer floor with the adjacent mucosa and on the other hand an elevated wall at the opposite side, then malignant ulcer can be diagnosed safely. This picture has not been seen in any of the 79 benign ulcers, but it was seen in 11 of the

11. Schindler, R., and Templeton, F.: Comparison of Gastroscopic and Roentgen Findings, Radiology **29**:472, 1937.

12. Konjetzny, G. E.: Der Magenkrebs, Stuttgart, Ferdinand Enke, 1938.

34 malignant ulcers. This is the classic picture of a type 3 carcinoma according to Borrmann's macroscopic classification.[13]

Large Tumor Nodes and Masses in the Surroundings.—The malignant ulcers in our series were all surrounded by some form of infiltration. Large tumor nodes and masses surrounding an ulcer are suggestive of a malignant lesion. Six of 34 malignant ulcers presented this picture, but it is important to note that 1 benign ulcer among the 79 cases studied showed a similar picture. In this case the anterior edge of the ulcer was entirely sharp, but the posterior edge could not be seen as it was covered by a large red hemorrhagic node of the posterior wall, and many other nodes in the adjacent mucosa suggested definitely a malignant lesion. The course proved that this impression was wrong. The case will be discussed later.

Irregular Ridges or Nodes Within the Ulcer Floor.—Irregular ridges or nodes within the ulcer floor were seen in 4 malignant ulcers but in no benign ulcer. Emphasis, however, has to be laid on the word "irregular." If one sees the floor of a large ulcer consisting of many regular nodules, one is inclined to make the diagnosis of carcinoma. This mistake was made by one of us (R. S.) in one of his earliest observations, and the respective case was pictured and published.[14] At that time the wrong diagnosis of carcinoma was made, but the following operation showed that the regular nodules were the lobuli of the pancreas, into which the ulcer had penetrated.

Diffuse Infiltration of the Whole Stomach, Even Without Visualization of the Ulcer.—Diffuse infiltration of the whole stomach, even without visualization of the ulcer, although encountered in only 1 case of malignant ulcer, is mentioned because of its great significance. Benign ulcer with considerable gastritis surrounding the lesion was diagnosed by roentgen examination, and for more than a year the clinical course was that of benign ulcer. However, at the first gastroscopic examination the whole gastric mucosa was seen to be stiffly infiltrated, although the ulcer itself never came into view. Malignant lesion was strongly suspected from this picture, but some rare kind of extensive hypertrophic gastritis or some other diffusely infiltrative lesion could not be excluded. At autopsy the entire stomach was stiffly infiltrated by carcinoma, and, retrospectively, it is entirely clear that diffusely infiltrative carcinoma was present from the beginning. In this case, the niche in the roentgenogram became small and almost disappeared during medical treatment;

13. Borrmann, R., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, pt. 1, p. 865.

14. Schindler, R.: Lehrbuch und Atlas der Gastroskopie, Munich, J. F. Lehmann, 1923.

this misled the clinician. Perhaps it would not have been wise to have made the gastroscopic diagnosis of malignant lesion after the very first examination, but when the stiff nodular infiltration persisted through several reexaminations the malignant nature of the lesion should have been apparent.

White Crystal-Like Floating Material of the Ulcer Floor.—Pathologists[13] have said that sometimes the floor of a malignant lesion is covered by necrotic dirty material which floats when held under a current of water. This floating may be observed by gastroscopy also when the stomach is inflated. But the material in such cases looks brilliant white and crystal-like. The floor of a benign ulcer may look brilliant white, too, and it may contain necrotic material, but the specific crystal-like floating appearance, according to our experience, is seen only in malignant ulcers.

Location in the Antrum Close to the Greater Curvature.—Some authors, especially Holmes and Hampton,[15] have emphasized that most prepyloric ulcers are malignant. In our series, out of 34 malignant ulcers, 17 were located in the antrum or prepyloric region. Three ulcers were in the greater curvature of the antrum and 3 in the anterior wall close to the greater curvature. Only 1 malignant ulcer was located on the lesser curvature and the posterior wall of the antrum. In 10 cases a diffuse lesion of the whole antrum was seen.

Out of 79 benign ulcers, only 5 were found in the antrum or prepyloric region. Of these, 2 ulcers were found in the lesser curvature; 2 in the anterior wall; and only 1 close to the greater curvature. In 1 case the wrong diagnosis of benign ulcer was made at the first examination. Location close to the greater curvature, unusual shape and bleeding of the edge should have cautioned the observer. This case will be discussed later. In order to diagnose benign ulcer in the antrum gastroscopically with certainty, especially if the ulcer is not located within the lesser curvature, it must not be associated with any sign which might question its benign nature.

Visible Ulcer in the Pylorus.—Benign ulcer of the pylorus usually distorts the pylorus so that it is drawn out of the field of vision and cannot be observed at the gastroscopic examination. If an ulcer is seen to be located in the pylorus, it is most likely malignant. This rule proved to be correct in 1 case of extremely small carcinomatous ulcer of the pyloric ring. This case has been described elsewhere.[16]

Bleeding of the Edge.—Bleeding of the edge of a malignant ulcer may be observed frequently during gastroscopic examination. We saw

15. Holmes, G. W., and Hampton, A. O.: The Importance of the Location in the Differential Diagnosis of Benign and Malignant Ulcerations, New England J. Med. **208**:971, 1933.

16. Schindler, R., and Gold, R.: Gastroscopy in Gastric Carcinoma, Especially in Its Early Diagnosis, Surg., Gynec. & Obst. **69**:1, 1939.

this in 6 of our cases. The benign ulcer usually does not bleed at all. If it is seen bleeding, the blood is more likely to originate from the base of the floor and to cover the whole ulcer. However, also in 2 benign ulcers, bleeding of the edge was observed, so that this is not a reliable, although a suggestive, sign of malignancy.

Dark Red Color of the Wall and Pale Surroundings.—It has been stated before that in both benign and malignant ulcers a wall is often present which may have the same color as the adjacent mucosa. But in 7 malignant ulcers in our series, this surrounding wall was found to be strikingly dark red in contrast to the pale surrounding mucosa. In none of the 79 benign ulcers was this characteristic picture found.

Fig. 3.—Unusually large ulcer niche. The benign nature of the ulcer was proved by the clinical course and by microscopic examination after autopsy.

Blending Edge.—While the typical benign ulcer has sharp edges on all sides, the floor of the malignant ulcer blends smoothly with the adjacent mucosa so that either nowhere or at a large portion of the circumference no definite borderline between the ulcer floor and the mucosa can be made out (fig. 1 *B*). Some blending of the edge, however, was seen in 3 benign ulcers of the 79, but in all 3 the blending area was only a few millimeters wide. Nevertheless, in 2 of these cases, this sign led to the wrong diagnosis of malignant lesion. These cases will be discussed later. Although they have taught us that the blending of the ulcer edge is not an absolute sign, we still feel that in such cases the definite diagnosis of benign ulcer should not be made. We feel that in these few cases indefinite or even wrong gastroscopic diagnoses are unavoidable.

Ulcerations in the Wall Surrounding the Ulcer.—Small ulcerations in the surroundings of a benign ulcer are rare. In only 3 cases of benign ulcer such small ulcerations were seen in the adjacent mildly inflamed mucosa. Never was such a small ulcer seen within the wall surrounding a benign ulcer, although such erosions occurred within the walls of 3 malignant ulcers. We have the definite impression that ulcerations within the wall are diagnostic of malignant ulcer. In 1 of our cases the correct diagnosis was based exclusively on this sign.

GASTROSCOPIC SIGNS WHICH ARE NOT PROOF OF MALIGNANT ULCERATION

Large Size.—In our series we had such a great amount of unusually large benign ulcers that we feel that large size is not even suggestive of malignancy in doubtful cases. The base of our largest benign ulcer was 51 mm. in diameter. Not less than 12 of the benign ulcers had a base of 25 mm. or more. On the other hand, small ulcers were seen in cases of gastric carcinoma.

Atrophic Gastritis.—According to former conceptions about the frequent occurrence of atrophic gastritis with carcinoma and the absence of this disease with chronic gastric ulcer, we have been inclined to decide in favor of carcinoma when we saw gastroscopically extensive outspoken atrophy. We had to abandon this criterion because we found benign gastric ulcers in which the gastric mucosa was almost completely atrophic. Some kind of atrophy, either patchy or complete, was seen associated with 19 of the 79 benign ulcers.

Infiltration of the Mucosa About the Ulcer.—It has been mentioned before that benign ulcer is frequently surrounded by an area of infiltration or by a callous wall. Therefore, these findings cannot be used in favor of a diagnosis of carcinoma. The mucosa about a benign ulcer was seen to be definitely infiltrated in 13 instances.

Callous or Edematous Wall.—A true circular wall may be present in both types of lesion. Such a wall was seen in not less than 7 of our benign ulcers.

Ragged Edge.—The sign of ragged edge is listed here for the sake of completeness. It has been mentioned before that the ragged or irregular edge of an ulcer must not be confused with the blending of the ulcer floor with the surrounding mucosa. The latter sign is pretty characteristic of a malignant lesion, but a benign ulcer may have an irregular and even ragged edge; this, however, shows sharp limitation between the ulcerated area and the mucosa at every point (fig. 4). It may even occur that benign ulcer, which at the beginning is completely round or elliptic may in the later development send out irregular protuberances which seem to creep into the previously normal mucosa and effect a rather grotesque and unexpected picture, which is different

from what is usually seen by roentgen examination. At the first examination, 5 benign ulcers presented the ragged appearance described.

Hill-Like Elevated Area.—One of us (R. S.) previously described this sign as characteristic of malignant lesion. This opinion cannot be held any longer. If the ulcer presents the usual signs of benignity then its location on an elevation does not disprove the diagnosis. Three of our benign ulcers were found to be located on hill-like elevations.

Necrotic Material on the Ulcer Floor.—If the beginner sees large amounts of necrotic material covering the ulcer floor, he is much inclined to diagnose a malignant lesion. This, however, is not permissible. In

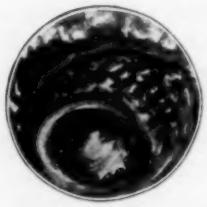

Fig. 4.—Gastroscopic view of a benign ulcer with a ragged edge. In spite of the stiff nodular infiltration of the surrounding mucosa and of the ragged edge, the benign nature of this ulcer can safely be diagnosed, because the edge of the ulcer is sharply cut out.

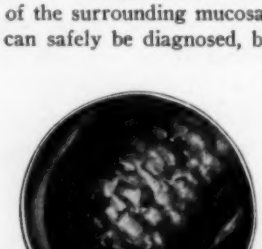

Fig. 5.—Gastroscopic view of an unusually large benign ulcer located on the lower posterior wall. To the beginner, the nodes of the floor would suggest a malignant lesion, but their regularity proves that they are the lobuli of the pancreas into which the ulcer has penetrated. Under medical care this ulcer healed completely within a few weeks.

cases of spastic retention necrotic food material sometimes is seen to be located on the floor of a benign ulcer. In our series this happened in 3 cases.

Regular Nodes of the Floor (Fig. 5.).—It has been mentioned before that former experience taught us that regular nodes of an ulcer floor may be the noduli of the pancreas into which the ulcer has penetrated. We found this sign in 1 case of our ulcer series, and it is listed here again because the beginner will regularly diagnose carcinoma when he sees this phenomenon.

ANALYSIS OF THE WRONG AND THE INDEFINITE GASTROSCOPIC DIAGNOSES

As mentioned before, in a series of 113 gastric ulcers visualized gastroscopically 6 wrong gastroscopic diagnoses were made, and in 2 cases no definite differential diagnosis was made. In the same series 7 wrong roentgen diagnoses were made, and in 15 cases no definite statement could be made after roentgen examination. In only 1 case both methods came to a wrong diagnosis.

The cases in which a wrong or indefinite diagnosis was made by gastroscopy will be reported briefly. The first 2 cases are cases in which a benign lesion was wrongly assumed to be present.

REPORT OF CASES

CASE 1.—It is important to note that in the one case in which the roentgen examination and the gastroscopic examination concurred in the wrong diagnosis of benign ulcer, the therapeutic procedure was not definitely influenced by this error. This case confirms Palmer's opinion that critical evaluation of all symptoms will lead practically always to correct therapy. The roentgenologist's impression was: "I doubt but cannot rule out the possibility of malignant lesion." The first gastroscopic protocol read as follows: "A large ulcer was seen in the anterior wall of the antrum at the level of the angulus. . . . It was not deep, but its diameter was at least 1.5 cm. The color of the floor was yellowish gray. The edge was perfectly sharp. At the lower portion of the ulcer toward the greater curvature there was a darkish red excavation within the floor of the ulcer. Small nodules surrounded the edge of the ulcer. The mucosa, however, did not show definite inflammatory changes. In the normal mucosa of the lesser curvature, 1 cm. above the ulcer, a small elliptic ulceration about 2 mm. long and about 1 mm. wide was seen. When the observation was continued, the anterior edge of the ulcer started bleeding spontaneously but only mildly. The other portions of the gastric mucosa were perfectly normal. In spite of the lavage of the evening before, a large amount of fluid containing food remnants and free hydrochloric acid was obtained."

In the impression the unusual shape and character of this sharply limited ulcer were emphasized. This, together with the clinical picture, led to careful observation of the patient, and three weeks later the gastroscopic impression was: "Today the ulcer looks carcinomatous. I believe this is a benign lesion, but the patient should be reexamined within a week because malignancy cannot be excluded absolutely, since it is amazing how the shape of this ulcer changed within a short time."

A definite wall-like elevation was seen at this time. After this report the patient was advised to undergo gastric resection. A rather small carcinoma with a large ulcer located in the antrum was found at operation, and successful resection was carried out. There can be little doubt that if we had applied the signs obtained from the previous analysis, either a correct or at least an indefinite diagnosis would have been made at the very first examination. The location of the ulcer in the antrum close to the greater curvature, the bleeding of the edge during the examination and the finding of a second small ulceration should have been interpreted in favor of the diagnosis of malignant lesion.

CASE 2.—In the second case in which a wrong gastroscopic diagnosis was made in favor of a benign lesion, the patient was a 55 year old man. At the first roentgen examination, the diagnosis was carcinoma. At a second examination the roentgenologist was unable to differentiate definitely between a benign and a malignant lesion. The gastroscopic impression was as follows: "The wall at the anterior side of the huge ulcer crater is higher than is usually seen in cases of benign ulcer. Nevertheless, the picture is not characteristic of a malignant lesion, and I believe that this may be a benign ulcer . . ."

The study of the gross specimen revealed why a wrong diagnosis was made by gastroscopy. It contained 2 ulcers; the second and smaller one had evidently been hidden behind the huge wall at the gastroscopic examination. The floor of this smaller ulcer consisted entirely of carcinomatous tissue, but in the greatest portion of the upper large ulcer there was no carcinoma visible, although some cords of carcinomatous cells were seen, especially at that margin which was directed toward the small carcinomatous ulcer. The impression was obtained that this large ulcer had been digested away from the carcinomatous tissue by hydrochloric acid, 90 units of which had been found in the gastric juice. It was unfortunate that a high wall hid the second ulcer and the carcinomatous infiltration. Even a biopsy taken during gastroscopy would have solved the problem only if accidentally a piece of the small region still showing carcinomatous infiltration had been cut out. In this case also clinical observation together with the unusual roentgen and gastroscopic reports led to the proper therapeutic procedure, namely, successful resection.

In the following cases the wrong diagnoses were made in favor of malignant lesion, but the lesion turned out to be benign ulcer.

CASE 3.—In this case an indefinite diagnosis was made after roentgen examination, but at the first gastroscopic examination the diagnosis of carcinomatous ulcer was made. The protocol read as follows: "A huge crater was seen in the lesser curvature above the angulus. There was a low wall toward the anterior wall of the stomach. The floor of the ulcer crater showed a dirty gray brown and reddish color and gray dirty necrotic material. A definite borderline between the ulceration and the gastric mucosa was not seen. The edges of the ulcer were bleeding. The surroundings were infiltrated. The impression was: There is carcinomatous ulcer, type 3 present. I do not believe this ulcer is benign." However, the indefinite roentgen diagnosis led to gastroscopic reexamination a week later. The protocol read as follows: "The necrotic material in the floor of the ulcer had disappeared. The floor now looked dirty gray, but the dirty gray ulcer was sharply limiited toward the mucosa . . . The angulus was arch shaped. The impression was: (1) The ulcer looks entirely benign today. (2) Henning's sign of the angulus is present."

After that, the patient was treated medically, and the further course proved the ulcer to be benign. Probably the mistake made at the first examination was unavoidable. But it is characteristic how close cooperation between clinician, roentgenologist and gastroscopist avoids a wrong course of therapy. The doubts arising from the roentgen examination led to a second gastroscopy through which the definite diagnosis of a benign ulcer became possible.

CASE 4.—This is the first case which taught us that tremendous nodular infiltration may be found in a benign ulcer. At roentgen examination the definite diagnosis of benign ulcer was made. The gastroscopic protocol read as follows: "The ulcer was seen on the lesser curvature. It was a brilliant white area, the posterior edge of which was overlapped by a large red hemorrhagic node of

the posterior wall and never came into view during the entire examination. The anterior edge was entirely sharp. In its surroundings many thick nodes were observed. The entrance to the antrum was oval shaped, narrow, slitlike and stiff. It could be moved by pressure on the abdominal wall but was not pliable . . . The impression was: There is an ulcer above the angulus, the anterior edge of which is sharp, but the entire circumference is never seen. There is tremendous thickening and stiffening of the antrum. This may be unusually severe inflammatory infiltration. However, it looks much more like submucous malignant infiltration or some other type of infiltrative process."

We have listed this case as involving a wrong gastroscopic diagnosis, but the protocol makes it clear that the picture was a most unusual one. The roentgen diagnosis of benign ulcer together with the gastroscopic observations of an unusual picture led to medical therapy, and at the following gastroscopic examinations the infiltration had disappeared, and the ulcer was readily recognized as benign. In this case now we should make a more indefinite diagnosis than we did in the protocol of the first gastroscopic examination.

Case 5.—This case is remarkable because in it a greater number of gastroscopic examinations revealed continuously changing unusual pictures and because at a time when at gastroscopy the ulcer began to look entirely benign, the roentgenologist was inclined to change his diagnosis of benign ulcer to that of malignant ulcer. The gastroscopic picture in the beginning was such that even applying the criteria gained by our analysis would not have been sufficient to prevent a wrong diagnosis. The gastroscopic protocol read as follows: "Above the angulus on the lesser curvature a crater-like punched-out ulceration was seen. Its diameter was 1.5 cm. The floor was smooth and gray white. Its edge was entirely sharp toward the anterior wall, the posterior wall and the cardia. But in a small area toward the pylorus, we were unable to detect a sharp limitation between the ulcer and the surrounding mucosa. The ulcer edge was not ragged, and the ulcer floor was definitely blending with the surrounding mucosa, though only at one point about 3 mm. wide. The surrounding mucosa, especially toward the anterior wall, was swollen and reddened. At the posterior side a protruding wall was observed. This wall was neither soft, velvety, nor edematous, but stiffly infiltrated and cast a shadow on the posterior wall at the upper edge. At the point where the upper edge of the wall touched the lesser curvature, about 2 cm. above the ulcer crater, 2 whitish ulcers were seen lying in an inflamed mucosa. . . . The impression was: "A crater-like ulcer of the lesser curvature is present which I am forced to call malignant." This ulcer, observed for more than two years at the time of writing by numerous roentgen and gastroscopic examinations, never healed completely. Its shape changed in the most peculiar way. Islands of the mucosa developed in its floor, and disappeared again. The course seems to prove that this was benign ulcer of an unusual type, although it seems necessary to watch this patient carefully.

Case 6.—This is the only case in which the wrong gastroscopic diagnosis of carcinoma led to operation. The case is remarkable because the patient had histamine-proved anacidity (single examination)[17] and at gastroscopy, almost com-

17. Palmer, W. L.; Kirsner, J. B., and Nutter, P. B.: Spontaneous Variations in Gastric Secretion in Response to Histamine Stimulation, Am. J. Digest. Dis. **7**:427, 1940. Palmer, W. L., and Nutter, P. B.: Peptic Ulcer and Achlorhydria, Arch. Int. Med. **65**:499 (March) 1940.

plete atrophic gastritis. The latter observation together with large ulceration of the posterior wall led to the wrong diagnosis of carcinomatous ulcer. The department of pathology of the Mayo Clinic made a careful examination of the microscopic material of this ulcer. The ulcer proved to be perfectly benign. Since we now know that extensive atrophic gastritis is compatible with the presence of benign ulcer, today we probably should not commit ourselves and should make an indefinite diagnosis.

In the 2 following cases an indefinite diagnosis was made at gastroscopic examination.

CASE 7.—At roentgen examination the following statement was made: "Gastric ulcer is present. If this ulcer is benign, there is considerable associated gastritis." The gastroscopic impression was: "1. There is an ulcer crater of the lesser curvature with a high nodular wall. 2. There is hypertrophic gastritis. 3. I am unable to differentiate between benign and malignant ulcer and advise reexamination." A month later the reexamination advised was carried out, and the impression was: "Although the ulcer looks benign, I am still not ready to exclude malignancy because of the unusually high and stiff nodular wall." In spite of these indefinite roentgen and gastroscopic diagnoses, medical therapy was instituted and led to the recovery of the patient.

CASE 8.—After roentgen examination the statement was made: "The shallowness of the ulcer suggests that this lesion may be malignant." The gastroscopic impression was: "I cannot commit myself definitely on this ulcer. Its aspect is that of a benign ulcer, but the stiff infiltration of its anterior border, which is extensive, does not look like the callous wall of a benign ulcer and suggests a malignant lesion. There is extensive atrophic gastritis of the upper portion of the stomach."

This patient had carcinoma of the cervix treated by radium and roentgen therapy with good results. It seems that the gastric ulcer was benign. However, the patient failed to return after four months of observation, so that no definite, final diagnosis could be made. But it seems fair to place this case among those in which there were wrong and indefinite diagnoses.

According to our present experience we probably would now make correct diagnoses in 2 of these cases. In 2 of them we would make an indefinite diagnosis. But probably in 4 a wrong diagnosis would still be made. Thus we have to admit that with our present experience there would still be 6 of 113 ulcers of which a definite correct differential diagnosis could not be made. By roentgen examination, however, the diagnosis in 22 cases was either incorrect or indefinite. The patient will profit most by the use of both methods, and we believe that if this procedure is applied in every case, then in practically no case will the correct diagnosis be missed.

SUMMARY

The gastroscopic symptomatology of 113 gastric ulcers has been analyzed; 79 of these were benign and 34 malignant. Although it must be admitted that in 6 of the 113 cases of ulcer a definite correct diagnosis could not be made by gastroscopy even now, the value of the procedure is obvious.

CRITERIA OF AN ACCEPTABLE OPERATION FOR ULCER

THE IMPORTANCE OF THE ACID FACTOR

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AND
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MINNEAPOLIS

The empiric surgical approach to the ulcer problem has come to an end. Out of fifty years of accumulated experience has come a mass of conflicting data with reference to the accomplishment of operation in the management of ulcer without a clearcut definition of the criteria of an acceptable operation. The cause of this confusion is not difficult to detect. There being no general agreement among clinicians or investigators concerning the cause of ulcer, the surgeon knew only that the objective of his craftsmanship was to prevent recurrence of ulcer; in determining how to attain that end, he had little or no help to guide him. Little wonder that the surgeon groped about aimlessly for procedures which he hoped might accomplish his objective of obviating recurrence of ulcer since he did not know how ulcer came about, what was demanded of a satisfactory operation or how his handicraft mediated its influence.

All this has changed. Accumulating evidence indicates clearly that acid is the important factor in the genesis of ulcer. It is not known what are the factors that condition the capacity of the gastric mechanism to secrete acid or what other factors may thwart or favor digestion of tissue by acid. However, that unneutralized hydrochloric acid secreted by the stomach may bring about the formation of ulcer is definitely established.

Bickel (1909),[1] Exalto (1911),[2] Langenskjöld (1914)[3] and Mann and Williamson (1923)[4] demonstrated successively that exclusion of

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1. Bickel, A.: Beobachtungen an Hunden mit exstirpiertem Duodenum, Berl. klin. Wchnschr. **46**:1201-1202, 1909.

(Footnotes continued on next page)

the bile and the pancreatic juice from entry into the duodenum at the usual site was an effective means of producing ulcer. The Mann-Williamson operation of diverting bile and pancreatic juice into a lower level of the intestine has become an effective agency of producing ulcer and of indicating the great importance of the acid factor in the origin of ulcer. By the interposition of a valve which prevented retrograde regurgitation of the contents of the transplanted segment into which bile and pancreatic juice are dumped, Matthews and Dragstedt [5] were able to bring about the formation of ulcer with performance of the Mann-Williamson operation at the new gastrojejunal outlet in 100 per cent of their experiments.

PRODUCTION OF ULCER BY THE STIMULATION OF GASTRIC SECRETION WITH HISTAMINE

With Code's [6] method of the intramuscular implantation of histamine in beeswax (to permit gradual liberation of the histamine), ulcer has been produced in this laboratory in a large number of animals. Histamine is a powerful stimulant of gastric secretion and apparently exerts its effect directly on the parietal cells responsible for the secretion of acid. Under the influence of the abnormal torrent of acid gastric juice provoked by the continuous and gradual release of histamine from the beeswax, the agencies which succeed ordinarily in achieving intestinal chyme with a neutral p_H in the upper reaches of the jejunum are outdone, and acid digestion of the stomach and/or the duodenum ensues with the formation of one or more ulcers.[7] These ulcers are similar in appearance to ulcers developing spontaneously in man. Hemorrhage, excavation, induration and perforation are common accompaniments. The experimental pro-

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2. Exalto, J.: Ulcus jejuni nach Gastroenterostomie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:13-41, 1911.

3. Langenskjöld, F.: Ueber die Widerstandsfähigkeit einiger lobender Gewebe gegen die Einwirkung eiweisspaltender Enzyme, Skandinav. Arch. f. Physiol. **31**: 1-74, 1914.

4. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409-422, 1923.

5. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **55**:265-286, 1932.

6. Code, C. F., and Varco, R. L.: Chronic Histamine Action, Proc. Soc. Exper. Biol. & Med. **44**:475-477, 1940.

7. Hay, L. J.; Varco, R. L.; Code, C. F., and Wangensteen, O. H.: The Experimental Production of Gastric and Duodenal Ulcer in Laboratory Animals by the Intramuscular Injection of Histamine in Beeswax, Surg., Gynec. & Obst., to be published. Walpole, S. H.; Varco, R. L.; Code, C. F., and Wangensteen, O. H.: Production of Gastric and Duodenal Ulcers in the Cat by Intramuscular Implantation of Histamine, Proc. Soc. Exper. Biol. & Med. **44**:619-621, 1940.

duction of ulcer by this means has served not alone to emphasize the great importance of acid in the genesis of ulcer; in addition, the method provides a simple means of producing ulcer in a variety of animals in which the development of ulcer may be studied together with factors which favor or retard the inception of ulcer as well as factors which favor or retard healing.

INFLUENCE OF FOOD RETENTION IN THE STOMACH ON THE PRODUCTION OF ULCER

It is to be recalled that ulcer develops spontaneously in man. As far as is known, at least in the common domestic or laboratory animals, spontaneous ulcer occurs by no means frequently. One of the factors which may bear on this issue is the rate of transit of food from the stomach. The human stomach is empty, normally, about seven hours after eating. The stomach of many laboratory animals cannot be relied on to be empty after twenty-four hours of starvation. The rabbit is a notable example. After days of starvation there may be food in the rabbit's stomach. The rabbit is one of the laboratory animals in which we have had difficulty in producing an ulcer with histamine in beeswax. More recently, by feeding 2 rabbits the pressed juice of ground carrots, cabbage and lettuce, we were successful in producing a large perforated duodenal ulcer in 1 (fig. 1 *D*). In the other rabbit, a large perforation involving a good portion of the entire length of the greater curvature of the stomach occurred. The experiments of Dragstedt suggested strongly the great neutralizing effect of food on gastric acidity. Dragstedt and Vaughn (1924) [8] failed to note evidence of the digestion of viscera implanted with an intact blood supply into the entire stomach of a dog. When, however, Matthews and Dragstedt (1932) implanted such viscera into isolated gastric pouches of dogs, into which food could not enter, digestion of the implanted living tissue occurred regularly.

The traumatizing effect of food in provoking gastric erosion has been overemphasized and the neutralizing effect of food on gastric acidity has not been emphasized enough. The acid factor is far more important in the genesis of ulcer than mechanical trauma by food.

METHOD

Since acid appears to be the most important factor in the genesis of ulcer, it is logical to infer that effective reduction of gastric acidity should be the first requirement of a satisfactory operation directed at the surgical relief of ulcer.

8. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies: The Resistance of Various Tissues to Gastric Digestion, Arch. Surg. **8**:791-810 (May) 1924.

We have looked on the attainment of achlorhydria (absence of free hydrochloric acid) as a desirable objective after operation, feeling that achlorhydria is incompatible with recurrence of ulcer. In this study no patient has been considered postoperatively achlorhydric unless free hydrochloric acid was absent in the gastric aspirations after three successive subcutaneous injections of 0.5 mg. of histamine hydrochloride.[9]

Gastric acidity was determined by the usual colorimetric titration; Töpfer's reagent was employed as the end point for free hydrochloric acid. We have come more and more to disregard the determination for total acidity as having any real significance. As was pointed out previously, the reading for total acidity includes also the capacity of protein to combine with a base, e. g., sodium hydroxide; in

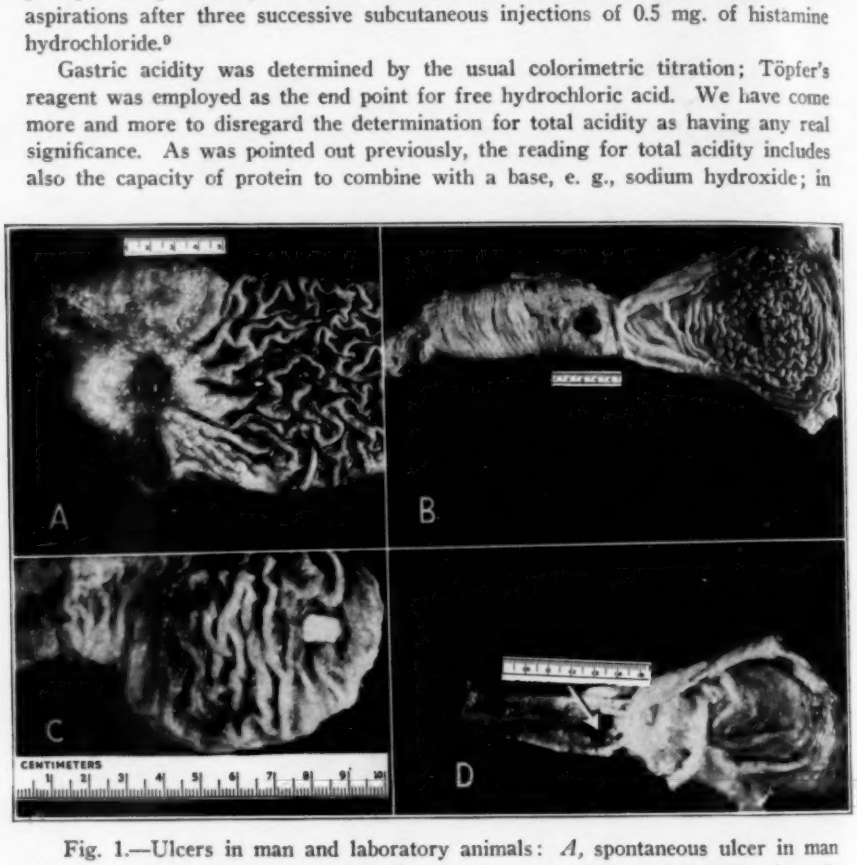

Fig. 1.—Ulcers in man and laboratory animals: *A*, spontaneous ulcer in man (resection specimen). The ulcer, perforating in type, caused serious hemorrhage in the antrum. *B*, ulcer produced in the duodenum of a dog by the intramuscular injection of histamine in beeswax. *C*, perforated gastric ulcer produced in a cat in the same manner. The gauze on the serous surface of the stomach can be seen plainly through the large perforation. *D*, perforated ulcer of the duodenum (at arrow) produced in a rabbit by the intramuscular injection of histamine in beeswax. The rabbit was fed the pressed juice of cabbage, carrots and lettuce.

consequence, the determination of total acids includes not alone the acid combined with protein but as well the buffering ability of the protein.

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9. Wangensteen, O. H.; Varco, R. L.; Hay, L. J.; Walpole, S., and Trach, B.: Gastric Acidity Before and After Operative Procedure with Special Reference to the Role of the Pylorus and Antrum: A Preliminary Report of a Clinical and Experimental Study, Ann. Surg. **112**:626-670, 1940.

Gastric acidity was determined regularly in the morning before the patient had breakfast. A no. 14 F duodenal tube with four perforations at the tip was introduced through the nose into the stomach. Continuous aspiration with the usual water suction siphonage apparatus was used through the period of the study. The following determinations were made at thirty minute intervals: (1) fasting; (2) after three successive subcutaneous injections of 0.5 mg. of histamine hydrochloride, each injection being made at intervals of thirty minutes. In an earlier study, the response to food and alcohol was elicited as well. Each test, as outlined, required that the patient remain for two hours. In the interests of conserving our own time, as well as that of the patients, we have come to rely largely on determinations of the fasting acidity (free hydrochloric acid) and the response to maximal stimulation with histamine (three successive subcutaneous injections of 0.5 mg. of histamine hydrochloride). These tests are performed frequently—when the patient leaves the hospital after operation (usually about the twelfth day) and again at intervals of six to eight weeks for the first six months and, thereafter, at three to four month intervals for an indefinite period.

The gastric emptying time (determined by the time required for complete gastric evacuation of 5 ounces [147.9 cc.] of ingested barium sulfate) has been followed in these patients. It is to be remembered, however, that, as indicated in an earlier study, the gastric emptying time is shortened almost invariably by all operations on the stomach.[9] In this study, therefore, no reference will be made to that aspect of the problem. Most of the patients have been subjected to postoperative gastroscopic studies, but these data have not been surveyed completely as yet. This study concerns itself largely, therefore, with the determination of which operations for ulcer are attended by effective reduction of gastric acidity.

EVALUATION OF OPERATIVE PROCEDURES ON THE BASIS OF THE EFFECTIVE REDUCTION OF GASTRIC ACIDITY

The types of operation evaluated and a summary of the results of the study are given in the table. It is to be noted that consistent achlorhydria to triple stimulation with histamine was not achieved after any type of operation. Judged on the basis of effective reduction of gastric acidity, there are essentially only two types of operation which appear to afford real promise of thwarting the acid-ulcer diathesis, viz., those done on the patients in groups 3 and 4 *A*. Gastrojejunal ulcer has not been observed after either of these procedures. Accepting attainment of achlorhydria as an important criterion of a satisfactory operation for ulcer, the remaining types of operative procedure must be rejected as unsatisfactory because they fail to meet the requirements of the test too consistently. Further, in groups 1, 2, 4 and 5, the incidence of gastrojejunal ulcer alone constitutes adequate reason not to recommend these procedures.

Patients who have undergone the three-quarter gastric resection performed on the patients of groups 3 or 4 *A* may eat anything; the imposition of dietary restrictions is unnecessary. Within four months after operation, usually, the gastric capacity of the majority of these patients has returned to normal, so that they can eat a full-sized holiday

dinner without distress. It is to be remembered that the thin-walled fundus is the most dilatable portion of the stomach. In the main, most of these patients hold their weight satisfactorily. A number gain weight. Some patients, who through years of rigid dieting have cultivated an aversion for dairy products, tend to lose a little weight. If such patients exhibit substandard weights, they are given a 3,000 calory diet slip and instructed that while they may eat anything, they should choose their articles of diet largely according to that guide.

The majority of our patients come from the rural areas of Minnesota and earn their livelihood by the toil of their hands. It is a real pleasure

Types of Operation for Ulcer and Postoperative Incidence of Achlorhydria and Gastrojejunal Ulcer

Group	Type of Operation	Patients	Patients Consistently Achlorhydric to Triple Stimulation with Histamine	Gastrojejunal Ulcer
1	Gastrojejunostomy	29	0	10%*
2	Antral excision, or the small gastric excision, with Polya anastomosis	6	0	2 (33%)
3	Three-quarter resection, including the pylorus and antrum with Hofmeister retrocolic anastomosis	82	52 (63%)	0
4	Finsterer exclusion operation, three-quarter resection, allowing 2 to 3 finger-breadths of the antrum to remain	12	3 (25%)	1 (8.5%)
4A	Finsterer exclusion operation with excision of the remnant of the antral mucosa	11	7 (63%)	0
5	Total intragastric regurgitation (Schmilinsky operation) after antral excision	3	0	2 (66%)
6	Tubular excision of the greater curvature (fundusectomy) with gastrojejunostomy	8	2 (25%)	0
7	Tubular excision of the greater curvature (fundusectomy) without gastrojejunostomy	5	0	0

* Only 29 patients were submitted to study after triple stimulation with histamine. In 138 patients who had gastrojejunostomy, gasrojejunal ulcer was observed in 14.

to observe the large number of these patients who despite years of inability to be economically self-sufficient because of inadequate relief on conservative ulcer management become rehabilitated completely by being rid of their ulcer diathesis by a satisfactory operation.

There are a few persons who are not constituted to admit subjective improvement after any therapeutic procedure, let alone operation, however much their objective gain in health belies their statements. In this series (groups 3 and 4 *A*) we observed 2 patients of this sort. Both of these men looked fit. Both, however, had long backgrounds of psychoneurosis. After operative relief from the physical suffering of ulcer, patients of this type need continued encouragement and reassurance to diminish their mental distress. Occasional occurrences of this sort emphasize the obligation not alone to be alert to detect evidences of

psychopathic personality in patients but also to continue the friendly ministrations of the physician.

No evidence of anemia or dietary deficiency has been observed in patients on whom the three-quarter gastric resection has been performed. Inasmuch as Castle (1941) [10] found that the fundus of the human stomach contains the intrinsic antianemic factor in abundance, it is not likely that anemia will follow such operations. Whether such patients will need particular notice with regard to iron and calcium requirements remains to be determined.

Our clinical experience suggests that the operative risk of the three-quarter resection for ulcer is between 2 and 3 per cent [11]—a mortality rate no greater apparently than that reported by other investigators employing the small antral resection, or the operation used on the patients in group 2. Every one will admit freely that there is no object

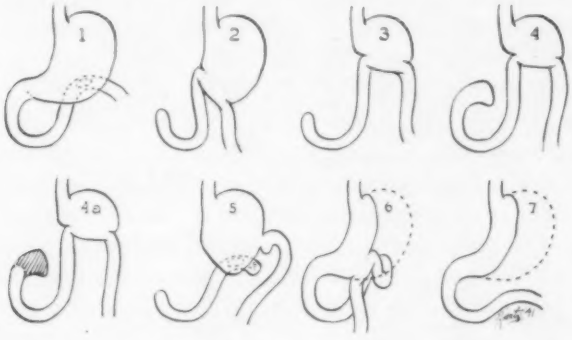

Fig. 2.—The various types of operative procedures performed on the patients in this study.

in excising more gastric tissue than is necessary to protect against recurrence of ulcer. The three-quarter resection satisfies this important requirement of an acceptable operation for ulcer; the operation used on the patients in group 2 does not. Whether resections intermediate in size will do away with the ulcer diathesis has not been determined. It has been pointed out before that even the three-quarter resection fails to make all patients uniformly achlorhydric to histamine stimulation.

In the surgical management of ulcer, it is to be remembered that the ulcer itself is not the disease but that it is only the end effect of unneutralized hydrochloric acid digesting away the wall of the stomach or the duodenum. It is the active gastric secretory mechanism which is respon-

10. Castle, W. B.: Stomach and Anemia, University of Minnesota Center for Continuation Study, March 1941.

11. Wangensteen, O. H.: The Surgeon and the Ulcer Problem, Illinois M. J. 80:100-110, 1941.

sible for the ulcer diathesis. Failure of operation to depress gastric secretion effectually compromises seriously the likelihood of the success of the procedure. There would appear to be some room for discriminating and effective choice among operations for ulcer, but there is little option between an acceptable operation and one which fails to meet the requirements of a satisfactory operation.

OBSERVATIONS CONCERNING THE VALIDITY OF THE EDKINS HYPOTHESIS

The operations outlined afforded an opportunity to submit Edkins' hypothesis (1906) [12] of pyloroantral control of gastric secretion to experimental scrutiny. It is to be noted that excision of the antrum (the operation done on the patients in group 2) fails to make patients achlorhydric. It was followed by gastrojejunal ulcer in 2 of the patients studied. Small gastric resections were done mostly as emergency operations for bleeding duodenal ulcer. During the last two years, the three-quarter gastric resection has been done under similar circumstances. The operation done on the patients in group 6 (fig. 2), in which the antrum is left, is not followed by a high incidence of persistent achlorhydria to triple stimulation with histamine. The satisfactory experience with operations done on the patients in groups 3 and 4 *A*, in which excision of the antrum accompanies extensive gastric resection, has been pointed out already. On the contrary, our experience with the operation performed on the patients in group 4, which differs from that done on the patients in group 4 *A* only in that the antral mucosa is excised in the latter, has been disappointing.

Case 1 throws interesting light on the relation of the antral mucosa to gastric secretion:

REPORT OF CASES

CASE 1.—E. H., a 42 year old man, was admitted to University Hospitals on April 1, 1940 with a typical history of duodenal ulcer of fourteen years' duration. For two years, the patient had been incapacitated by pain and unable to work. For eight months prior to admission, he had been subjected to a strict medical regimen which included administration of a colloidal suspension of aluminum hydroxide and medication with phenobarbital, without material improvement. There had been no antecedent perforation or massive hemorrhage.

On physical examination, there was evidence of slight exophthalmos, but the basal metabolic rate was normal. On gastric analysis, free acid was 90 degrees in the fasting specimen and 112, 122 and 110 degrees, respectively, in specimens taken thirty, sixty and ninety minutes after the injection of 0.5 mg. of histamine. On roentgen examination, a defect typical of duodenal ulcer was found. On April 3, a Finsterer antral exclusion operation with extensive (three-quarter) gastric resection (group 4) was performed. Three fingerbreadths of the antrum

12. Edkins, J. S.: The Chemical Mechanism of Gastric Secretion, J. Physiol. **34**:133, 1906.

proximal to the pyloric sphincter was allowed to remain. The size of the resected gastric segment was 301 sq. cm. Closed (aseptic) anastomosis of the Hofmeister type was made. Convalescence was uneventful, and the patient left the hospital fifteen days after operation.

The patient was followed in the outpatient department. Epigastric pain recurred and was most severe at night. Over a period of ten weeks, gastric analysis was performed on four occasions, and free hydrochloric acid was found each time, once as high as 56 degrees with histamine stimulation.

Roentgen examination failed to reveal any evidence of gastrojejunal ulcer. On gastroscopic examination, several areas of erosion were detectable. It was believed that these were due to sloughing of the interrupted silk sutures in the inner row. (In the last twenty months, a running suture of catgut has been used for the inner row in all gastric resections. The outer row, however, is constituted of interrupted Halsted mattress sutures of fine silk.) Because of the persistence of symptoms and the continued presence of free hydrochloric acid in the gastric juice, the patient was admitted for excision of the residual antral segment. This operation was done on October 10. Closure of the duodenum was difficult. Temporary duodenal fistula developed, and this prolonged the hospital stay. On November 26, the patient was dismissed. In the early months of convalescence, free hydrochloric acid was found three times by gastric analysis; the highest value was 24 degrees and the average 12 degrees.

At the time of writing, the patient has been consistently achlorhydric (on three occasions during the past nine months), even to maximal stimulation with histamine (three successive doses of 0.5 mg. of histamine given at half hour intervals). The patient has been asymptomatically free from distress, and gastroscopic and roentgen examinations fail to disclose any evidence of recurrent ulcer.

Summary.—A man 42 years of age with a history of duodenal ulcer of fourteen years' duration was submitted to the Finsterer exclusion operation. He failed to become achlorhydric and continued to have symptoms. After excision of the antral segment and the pylorus together with a small fragment of the duodenum (the area of the entire mucosal segment excised was only 24 sq. cm.), the patient has remained achlorhydric and has become symptom free. Objectively, no trace of recurrent ulcer remains.

This occurrence speaks significantly for the presence of a pyloro-antral hormone. In the portion of the antrum removed in the first operation, Dr. Robert E. Hebbel, pathologist in University Hospitals, described the presence of extensive antral gastritis. There was dense interstitial lymphocytic infiltration of the mucosa. It is significant that in the antral segment removed at the second operation (six months later) all evidence of interstitial mucosal antral gastritis had disappeared.

This patient (case 1) exhibited no objective evidence of gastrojejunal ulcer after the first operation. In another patient (case 2), however, gastrojejunal ulcer developed after the Finsterer exclusion operation.

Case 2.—T. B., a man 40 years of age, was subjected to the Finsterer exclusion operation (group 4). Demonstrated gastrojejunal ulcer developed (table). Three months later the residual antral segment was excised. The area of the mucosal antral segment was 16 sq. cm. Achlorhydria did not develop. Hemorrhages from the gastrojejunal ulcer continued.

Three months after the second operation and six months after the initial Finsterer exclusion operation (Nov. 18, 1940), gastric resection was done in which the gastrojejunal ulcer was excised. The patient became achlorhydric at once and has continued symptomatically well.

It is needless to relate that we have ceased to use the Finsterer exclusion operation (group 4).

HISTAMINE CONTENT OF GASTRIC MUCOSA IN MAN

Gavin, McHenry and Wilson (1933) [13] studied the histamine content of the gastric mucosa in the dog and observed that the fundic mucosa is richer in histamine than that of the pylorus. They concluded that 80 per cent of total histamine content of the dog's stomach is to be found in the pylorus. Code and Trach [14] studied the histamine content in the mucosa of human stomachs resected for ulcer or carcinoma, making comparisons between the histamine content of the antral and the fundic mucosa. In cases of carcinoma of the stomach, sections of mucosa were dissected off the underlying muscle for study in areas where the gross appearance of the mucosa was fairly normal.

No significant differences in the histamine content of the gastric mucosa were observed in patients with ulcer or carcinoma of the stomach. Per unit of weight of tissue, the histamine content of the fundic mucosa exceeded that of the antrum. Subcutaneous injection of these mucosal extracts into dogs with prepared gastric pouches elicited somewhat comparable responses; in the main, the antral mucosal extracts produced the greater effect.

These observations of Code and Trach, when correlated with those made concerning the validity of the Edkins hypothesis based on the data concerning the operations done on the patients in groups 2, 4, 4 *A* and 6, suggest that the antral mucosa may contain a hormonal stimulant of gastric secretion other than histamine. Certain it is that excision of the antrum is necessary to achieve consistent achlorhydria after the three-quarter gastric resection in man.

PROTECTIVE INFLUENCE OF OPERATIVE PROCEDURE AGAINST THE HISTAMINE-PRODUCED ULCER

We propose to submit all the operative procedures described, which are designed to alleviate ulcer in man, to experimental scrutiny, employing the histamine in beeswax method of producing ulcer in dogs. As yet,

13. Gavin, G.; McHenry, E. W., and Wilson, M. J.: Histamine in Canine Gastric Tissues, J. Physiol. **79**:234-238, 1933.

14. Code, C. F.; Trach, B., and Wangensteen, O. H.: The Histamine Content of Gastric Mucosa, unpublished data.

we have had occasion to assess the results of only three operative procedures, viz., those used in groups 1, 2 (fig. 3) and 3. The intramuscular implantation of histamine in beeswax following the performance of the operation used in group 1 or 2 is regularly attended by anastomotic ulcer in the dog; on the contrary, such anastomotic ulcer has not followed the operation used in group 3 after the administration of histamine in beeswax. This phase of the study is still in progress, and a complete report cannot be made at this time. The preliminary observations appear to corroborate the findings of the more complete study on patients with reference to the merit of operations in effectually reducing gastric acidity.

Fig. 3.—Gastrojejunal ulcer occurring in a dog on which the operation (antral excision) done on the patients in group 2 had been performed prior to the intramuscular injection of histamine in beeswax. Similar ulcers have been observed after the operation done on the patients in group 1 but not after the operation done on the patients in group 3.

SUMMARY AND CONCLUSIONS

Acid is the most important factor in the genesis of ulcer. By stimulating the intrinsic gastric secretory mechanism with histamine in beeswax, from which histamine is liberated slowly, ulcer may be produced in a large number of laboratory and domestic animals.

The most important criterion of an acceptable operation for ulcer is that it reduces gastric acidity effectually. On this basis of the eight types of operation subjected to scrutiny in this study, only two (operations 3 and 4 *A*) appear to meet the requirements of a satis-

factory operation. The objectives of an acceptable operation are: (1) that it relieve the patient subjectively and remove the ulcer diathesis; (2) that it prevent recurrent ulcer; (3) that it do not compromise the future for the patient.

It appears that extensive removal of gastric tissue (three-quarter resection) is necessary to insure achlorhydria and to give assurance of meeting the first two requirements of an acceptable operation. Observation suggests that the achlorhydria of the three-quarter resection, so desirable to protect against recurrence of ulcer, meets adequately the third requirement of an acceptable operation, in that these patients lead active useful lives without evidence of any deficiency disorder.

The ulcer itself is not the item that should command the attention of the surgeon. It is the ulcer diathesis of the gastric secretory mechanism which demands his notice. The ulcer is merely the end effect of an overactive gastric secretion of acid. The only known manner in which the secretion of acid may be depressed effectually is by sacrificing a liberal portion of the gastric mucosa.

In order to insure achlorhydria, excision of the antral mucosa is mandatory. It is suggested that the antral mucosa may contain a hormonal stimulant of gastric secretion other than histamine.

SURGICAL TREATMENT OF DUODENAL ULCER

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Although it is now generally conceded that duodenal ulcer is a functional disorder and responds well to conservative measures, complications develop which require surgical intervention. Approximately 80 per cent of the patients with this lesion are taught to live in such a manner that they are comfortable and able to do their usual work. These persons may be successful in keeping completely symptom free if they refrain from worry and strain, eat properly and eliminate the use of tobacco, alcohol and condiments. Infringement of these rules may bring about recurrence or chronicity, which may well produce a situation that must be handled surgically. It is fair to say that a small percentage of these patients get into trouble in spite of rigid care. They are usually the victims of ulceration in an area that gives no warning of activation until massive hemorrhage or perforation takes place. Whether such a painless area exists in the duodenum of every human being is doubtful. There are, however, a considerable number of people who do have a silent area or whose lesion fails to produce the usual signs of activity, such as pain, heartburn and pylorospasm. Doubtless, the surgeon would see fewer patients in this group if the victim received the physical warnings that come to the average patient with ulcer. The index of discretion is well catalogued in the minds of the majority of such persons.

Less was known concerning the complex mechanism involved in the production of duodenal ulcer when operation directed toward relief of the condition became popular. Rest cures were not in vogue at that time. Hyperacidity was correctly believed to be the chief cause, but it took a long time to learn that there were other important contributory factors. If the early operations, conceived to produce a better neutralization of the gastric juice by the alkaline secretions of the liver and the pancreas, had been permanently successful and the operative mortality eliminated, it is doubtful if clinicians would ever have developed the understanding of the situation as it exists today. During this period of trial and error many types of operative procedures were devised. The immediate results of each new operation were excellent and were hopefully grasped as they were introduced; each advocate offered a good argument along

physiologic and mechanical lines. The terrible conditions which ultimately developed in so many of the victims of these procedures were indeed discouraging. So often a bad situation was turned into a frightful one, and no operation could ever be entirely without immediate risk. Under these circumstances, it is not difficult to understand how welcome has been the excellent progress of the internist, who has successfully developed a regimen that eliminates the need for operation in the majority of patients with duodenal ulcer. This leaves for surgical treatment approximately 20 per cent of these patients who come to a large urban general hospital. Acute perforation, massive hemorrhage, stenosis of the duodenum or the pylorus and intractability represent the complications of ulcer that are best treated by surgical methods.

ACUTE PERFORATION

Sudden perforation of duodenal ulcer is associated with a characteristic chain of symptoms and signs. Occasionally, the diagnosis is confused with renal colic in patients who have been liberal users of sodium bicarbonate, although the location and the radiation of pain and abdominal palpation should and usually do prevent error. Acute cholecystitis, acute appendicitis with perforation and acute pancreatitis also may be strongly considered in the differential diagnosis. As a matter of fact, the picture is usually clearcut, and even in the presence of difficulties of language one should have little trouble in arriving at the correct conclusion. Pain is severe and nearly always epigastric; collapse and shock of varying degrees are present. The pulse becomes elevated and the upper part of the abdomen rigid. Leukocytosis develops early. Roentgenograms of the abdomen taken with the patient in an upright position will show gas below the diaphragm in a large percentage of the cases.

The patient should be subjected to operation as soon as suitable conditions are available, since the earlier the perforation is closed the lower the mortality rate. Simple closure of the perforation is certainly the procedure of choice. This, I believe, is best done by Graham's[1] method of loosely fixing an omental tab over the perforation. This graft may be free or attached and is held in place by sutures passed above, below and through the ulcer site. Graham[2] reported only 2 deaths among 60 consecutive patients treated in this manner. This is the lowest published mortality rate that I have seen. Is the method of closure alone responsible for these excellent results? One must certainly give the method credit for its simplicity and rationale. This series did

1. Graham, R. R.: Perforated Ulcer, Surg., Gynec. & Obst. **64**:235-238, 1937.
2. Graham, R. R.: Technical Surgical Procedures for Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **66**:269-287, 1938.

not include only cases in which the risks were good and the perforations were recognized early. Doubtless, a coordinated effort in preoperative treatment and postoperative care played a large role in the successful outcome in this group of cases.

The choice of anesthesia is important. This is a poor operation with which to use inhalation anesthesia unless suction is maintained on a previously introduced Levine tube. At all costs, one must prevent inhalation of the stomach contents during operation. Although many of the patients do not vomit, some are apt to do so as soon as administration of the anesthetic is started, particularly if the anesthetic is of the inhalation variety. The tube should be introduced into the stomach before operation and kept there for several days afterward, regardless of the type of anesthesia used. Spinal and local anesthesias have their champions, and between them there is little choice, provided each is used correctly.

Care should be used to aspirate the fluid from the abdominal cavity. It is particularly useful to remove the collection from above the liver, for this diminishes the chance of subdiaphragmatic abscess. If there has been much delay in operation or there is an abnormal amount of extravasation of the contents of the stomach and the duodenum, it may be well to remove this material from the pelvis. This is best done by making a suprapubic stab wound, and then while the intestines are protected by the left hand from the upper wound, the suction tip can be introduced into the pelvis through the lower. If one is tempted to drain the abdomen under these circumstances, the wicks through the lower wound into the pelvis should be removed within forty-eight hours. The danger of obstruction of the small bowel is more serious than that of the development of a pelvic abscess. One must be careful not to introduce a drainage tube or wick to the site of the perforation since it is almost sure to produce a duodenal fistula. If one feels it necessary to drain the region, such drainage should be established in the subhepatic pouch of Morrison. The introduction of sulfanilamide powder into the abdomen after this and other operations on the duodenum is becoming popular. It will take some time to interpret the results of this use of the drug, but one must not rely on it as a substitute for good technic and after-care.

Closure of the perforation by suture has been the usual procedure. When one sees the wide extension of the induration about such an ulcer, it seems incredible that suture has met with its usual success. I feel that one of two things often happens—either the sutures infold so much of the area that obstruction takes place or they gradually give way while nature closes the opening by secondary adhesions to neighboring structures. Excision of the ulcer with closure of normal tissue has

been recommended by some operators. This I know to be unnecessary, and it does not meet with any better results than more simple procedures. Others have advocated a radical subtotal gastrectomy at this time. I believe that this operation, as well as concomitant gastroenterostomy or pyloroplasty, is unwarranted for this type of extremely ill patient. Any procedure should be looked on as a life-saving measure.

There is some evidence that one might consider conservative measures only in the treatment of acute perforated ulcer. This is based on the facts that Wangensteen suction, intravenous feedings and other measures will enhance healing of the ulcer and that peritoneal contamination will be cared for under a regimen of physiologic gastrointestinal rest. I have had slight experience with this type of treatment, but I feel that one can more safely carry out these measures after the leak has been stopped. It will take much courage and some years of experience to be able to show that the results with these conservative methods alone are comparable to those with the combination of closure and logical after-care.

That patients who have survived closure of a perforated ulcer should have at a time of election a radical procedure I may in time advocate, although my present studies do not warrant making this a blanket recommendation.

CICATRICIAL STENOSIS

During the healing process associated with repeated recurrence or the prolonged activity of duodenal ulcer, scar tissue may be formed in such a fashion as eventually to obstruct the outlet of the stomach. This occurs usually after the age of 60 and often after a considerable respite from acute symptoms. The onset is apt to be gradual, and the patient may enter the hospital with marked chronic dilatation of the stomach. In such cases, acidity is likely to be normal or even low. This low acid level in the opinion of Ochsner, Gage and Hosoi [3] is due to the effect of prolonged gastritis on the acid cells. Such patients must be accepted for operation, or starvation will take place.

It has been generally agreed by surgeons of experience in this field that this is the one remaining situation created by duodenal ulcer that warrants a palliative short circuit type of operation. Certainly, the prompt relief afforded by pyloroplasty, gastroduodenostomy, or gastroenterostomy is convincing. I [4] have advocated posterior gastroenterostomy for use in this situation as being the simplest and safest procedure

3. Ochsner, A.; Gage, M., and Hosoi, K.: Treatment of Peptic Ulcer Based on Physiological Principles, Surg., Gynec. & Obst. **62**:257-274, 1936.

4. Allen, A. W., and Welch, C. E.: The Role of Surgery in Peptic Ulcer, South. M. J. **31**:418-425, 1938; Peptic Ulcer Considered from a Surgical Point of View, New England J. Med. **220**:103-106, 1939.

I had used. I have now come to look on this operation, even for this type of patient, with some misgiving. In at least 2 men in late life, who had brilliant relief of disability after posterior gastroenterostomy which I did for cicatricial obstruction, jejunal ulcers have developed. One, past 80 years of age, bled acutely and alarmingly from his stomal ulcer. Each of these catastrophies followed the death of the patient's wife, after which the usual restrictions on the use of alcohol and tobacco were abandoned. It is my belief that restoration of function of the stomach allows a return of the usual acid activity and thus brings about the earlier vulnerability of such persons. It illustrates well the old dictum that "once an ulcer patient, always an ulcer patient," and the patient cannot break training even after cure by the physiologic changes of old age and the temporary reduction of acid by gastritis.

In patients in this group who present good risks, I am inclined to attempt a slow careful preparation. This includes Wangensteen suction for a few days and then physiologic rest of the stomach as described by Peters,[5] who has brought to attention the fact that the secretions of the salivary and the stomach glands will pass through an almost completely obstructed pylorus provided the stimulation of extra secretions by water and food or an inlying tube are withheld. Performing jejunostomy for feeding in such a patient will make it possible to delay operation until a proper chemical and fluid balance will permit a more radical operation. In treating the less elderly patients of this group, i. e., those between 50 and 70, I feel that serious consideration should be given to the possibility of subtotal gastrectomy rather than gastroenterostomy. This should be particularly thought of in treating the person who has found it difficult to live with his ulcer prior to the time of obstruction by scar tissue. Whether one decides on conservative posterior gastroenterostomy or a more radical operation, it is wise to decompress the stomach a few days before surgical intervention is undertaken. If gastroenterostomy is done, a slightly longer loop should be used, since the stomach will contract after the short circuit is made, and a poor stoma may result.

One should be careful not to confuse the group of patients just discussed with those with edematous obstruction frequently seen with reactivity of duodenal ulcer. These patients come into the hospital with complete obstruction, to be sure, but they are easily differentiated from those of the other group. As a rule they are younger and have a history of rapid recurrence of symptoms. Such patients after treatment by continuous suction for a few days followed by complete elimination of secretory stimulation will be able to take a thin diet in a week or ten

5. Peters, J. P.: The Structure of the Blood in Relation to Surgical Problems, Tr. Am. S. A. **58**:8-16, 1940.

days. These patients will soon reach a quiescent stage and on a careful regimen may even carry on indefinitely. I once felt that it was best to advise radical operation for patients in this group at a time of election. One should wait until the ulcer is well healed before undertaking a surgical procedure since the induration spreads to surrounding structures to an alarming degree. If one operates too early, it may be necessary to plan a two stage procedure or accept an unwarranted hazard with the duodenal stump. It often happens that by the time such a patient is judged ready for a radical procedure, he is symptomatically and objectively well. Under such circumstances, it is easy to be persuaded to allow the continuation of, or the establishment of, a sound conservative regimen.

MASSIVE BLEEDING

Approximately one third of all patients admitted to the wards of the Massachusetts General Hospital with duodenal ulcer have had gross bleeding. Of these, 36 per cent had sufficient loss of blood to produce severe anemia. Two thirds of those in the group with severe bleeding bled acutely in massive amounts. Actually, there were 94 such patients in the decade from 1923 to 1932,[6] a period during which 1,002 patients with duodenal ulcer were admitted to the wards. Of these 94 patients with acute hemorrhage, 13 bled to death. In a check of the situation from 1933 to 1941 in the same institution I found there had been 80 patients with acute severe hemorrhage, 9 of whom died. Thus, more modern management appears to have little effect on the mortality rate in this clinic.

In a study of this situation for the twenty year period prior to 1933, Benedict and I analyzed all the factors contributory to fatal massive hemorrhage from duodenal ulcer in 138 patients admitted to the hospital during that period.[7] We found, much to our surprise, that chronicity, repeated episodes of bleeding and most of the concomitant diseases had little relation to the fatalities. We expected that the patients with chronic, callous ulcers of long standing would be the type that would not spontaneously recover. The duration of symptoms in the recovered group was seven and seven-tenths years as against eight and one-tenth years for the group in which the patients succumbed to hemorrhage; this is not enough difference to approach even nearly the discrepancy in the age groups of those who recovered or died. The factor of repeated episodes of bleeding, which we thought would throw light on the subject, also was surprising; we found that in 9 of 20 cases in which

6. Allen, A. W.: Acute Massive Hemorrhage from the Upper Gastrointestinal Tract, Surgery **2**:713-731, 1937.

7. Allen, A. W., and Benedict, E. B.: Acute Massive Hemorrhage from Duodenal Ulcer, Ann. Surg. **98**:736-748, 1933.

death occurred, there had been no bleeding previous to the final admission. Ten patients had bled only once before, and 1 patient was admitted for his fifth episode of bleeding. Five of the patients who died had used alcohol to excess.

The Age Factor.—The age difference between the patients who recovered spontaneously and those who died was really the most striking finding in this study. The average age of those who died was 56.3 years as against 41.8 years for those who recovered. Actually, there were 2 deaths of patients under 49 years of age. The other 18 fatalities were of patients of or beyond this age. There were more than twice as many patients in the younger as in the older age group. In the past eight years (Jan. 1, 1933 to Jan. 1, 1941), only 1 patient of the 9 who died was under 50 years of age, and he was 44. In the spring of 1941, a man of 30 did succumb to massive hemorrhage from duodenal ulcer. I believe that I am justified in making some definite conclusions from these data. Certainly, those patients with enough arteriosclerosis to interfere with adequate thrombus formation in the bleeding vessel should be considered in a different category from those in the younger age group. Actually, in my experience the chance of the spontaneous recovery of those under the age of 45 was about 95 per cent, while for those beyond the age of 50 the chance was reduced to about 70 per cent.

Therefore, I believe that the younger patients should be treated conservatively until they have made a complete recovery; after this I advise a radical operation. This opinion is based on the fact that many of the patients who bleed severely get little warning of activity before sudden loss of blood takes place; moreover, their ulcers penetrate deeply and frequently are difficult to keep pain free. One should change the term "advise operation" to "urge operation" for patients beyond the age of 45 who have recovered spontaneously from severe massive hemorrhage. This policy should be extended to those who bleed without warning of renewed activity and to those whose hemorrhage occurs while they are submitting to a logical ulcer regimen, regardless of age.

Each patient beyond 45 years of age should be immediately hospitalized and his condition carefully evaluated. If there is doubt concerning the source of the bleeding, a fluoroscopic examination should be made as soon as the patient has recovered from shock. This requires the ingestion of only a small amount of barium sulfate, and with Hampton's[8] technic the crater can be easily visualized without palpation. I have seen no harm from any examination of this type made during the active phase of hemorrhage. Actually, these victims bleed intermittently, as can be determined from the pulse rate and the blood pressure charts; each new

8. Hampton, A. O.: A Safe Method for the Roentgenological Demonstration of Bleeding Duodenal Ulcer, Am. J. Roentgenol. **38**:565-570, 1937.

burst of bleeding causes the typical signs of shock. There are a variety of factors that enter into such a picture, and one may feel that a certain patient—judging from his robust appearance and the softness of his peripheral vessels—will spontaneously cease to bleed. As a matter of fact, many patients have only one severe hemorrhage and no subsequent bleeding during the episode. Others will have bursts at intervals of four to twenty-four hours, either prior to admission or while under observation. If these patients are somewhat arteriosclerotic but otherwise present good risks, there is no reason to permit them to succumb to hemorrhage. The decision for or against operation must be made early, and that means within seventy-two hours after onset. If operation is undertaken before the effects of starvation are present, the outcome will be successful. If one postpones surgical intervention until it is obvious that the patient will die of hemorrhage, the chance of success is small. Having made the decision to try conservative treatment, one should not, after a week or more of intermittent bleeding to repeated shock levels, be persuaded to attempt operation. Such a patient will survive the procedure nicely only to succumb to infection or pneumonia a few days later. I have proved that this is true of the older patients. It might be possible to rescue such a patient if the absence of food absorption could be counteracted or to save a young patient who might be expected to recover spontaneously.

Should operation be decided on in the early days of acute massive hemorrhage, one must approach the problem in a logical manner. As soon as the bleeding vessels are ligated, the patient should be supported by sufficient blood to replace his loss. The anesthesia should be spinal or local, since inhalation anesthesia is even more dangerous to a person in this depleted state than to the average person of his age. The operation should be planned to interrupt the three contributaries to the gastroduodenal artery lying behind the duodenum and transversing the head of the pancreas. This, I believe, is best done by transecting the stomach and approaching the vessels from the under side of the pyloric region as previously described. I have successfully accomplished this in 5 patients with duodenal ulcer and 3 with gastric ulcer who experienced acute massive bleeding and were operated on in the early days after onset. All of these patients were over 50 years of age. I have recently failed in operating on an elderly man; he had been bleeding ten days, and I should not have been tempted to operate on him. He died of bronchopneumonia on the sixth postoperative day. Another failure occurred in the case of a man of 60 owing to perforation of the ulcer three days after modified subtotal resection for exclusion. I successfully stopped the hemorrhage but made the mistake of freeing the lower segment of the duodenum before determining that the ulceration extended from

the pylorus to the bile ducts. The antrum was then transected and its mucosa removed. At autopsy, all suture lines were tight, but the huge 2 cm. ulcer had perforated into the free abdominal cavity. This patient had been successfully brought through resection of a gastrojejunocolic fistula two years before and had been urged to submit to subtotal gastrectomy one year prior to his last admission during a phase of activity of the original duodenal ulcer. In retrospect I see that I should have been able to determine by the extent of the inflammatory reaction that resection beyond this huge ulcer would be hazardous and that I should have contented myself with the resection as carried out without disturbing the adhesive protection about the ulcer site. It further bears out the fact that radical gastrectomy should be performed on patients with gastrojejunocolic fistula as a final stage of their treatment, for protection against recurrence of the original duodenal ulcer.

I am not in accord with the principles set down by some of my colleagues regarding early operation for acute massive hemorrhage in patients of all age groups. I admit that the younger patients are more likely to survive radical procedures than the older ones; likewise, I agree that these patients can be saved a good deal of time by immediate operation. On the other hand, I feel that with a large number of such operations one must expect a mortality rate of over 5 per cent, a figure that is too high for subtotal gastrectomy of election. Furthermore, it can be expected that at least 95 per cent of the younger patients coming to the hospital will cease to bleed spontaneously. It is fair to say that the time lost to the patient in getting into proper condition for a radical operation plus the small chance that bleeding will continue plus the ultimate operative mortality during a quiescent period all add up to a tempting argument.

There is a group of patients with duodenal ulcer who do not bleed acutely in massive amounts but whose blood loss is gradual and sufficient in quantity to cause marked anemia. These persons do not have a large open vessel but bleed from numerous smaller ones in and about the ulcer site. This type of bleeding is often associated with some pyloric obstruction. Occasionally, such a patient will require surgical intervention in order that proper feeding can be carried out. Under these circumstances, the patient is often in such a depleted state that some two stage operation is indicated. Most of the patients in this group will respond to a careful hospital regimen and finally cease to bleed and regain a normal state of health. Rarely, however, does a patient of this type remain symptom free. For this reason the patient should, at a time of election if possible, be subjected to radical subtotal resection.

INTRACTABILITY

Duodenal ulcer is intractable in a variety of cases. These cases represent approximately only 5 per cent of all cases of duodenal ulcer. They are difficult to define since so many factors enter the picture.

The location of the ulcer probably accounts for the intractability in the majority of the cases. Three sites are of importance: 1. When the ulceration is close to or actually involves the pylorus itself, there occurs a condition not unlike an anal fissure. As the pylorus opens and closes, there is a tendency to slow healing, and frequently the respites of comfort are of short duration. 2. An ulcer that penetrates deeply into the pancreas may not erode a large vessel as ulcers often do, but such a deep erosion is prone to heal slowly or recur frequently. The pain referred through to the back is often characteristic of such a lesion. 3. Graham [2] has described a "duodenal ulcer occulta" located on the posterior wall of the descending limb of the duodenum. An ulcer in this area is difficult to show in a roentgenogram and sometimes involves the biliary ducts. Often it is associated with a high transverse stomach in a moderately fat barrel-chested person. Accurate diagnosis may demand surgical exploration. I have seen patients with such ulcers living on a careful regimen and unable to become symptom free. The absence of roentgen confirmation is often disturbing, and an attempt may be made to explain the situation on the basis of a small hiatal hernia or disease of the biliary tract.

Economic factors often make it difficult to keep a patient with an ulcer free of discomfort. If a man has a family to support or has any self respect, he must keep at his job. It is easy enough to say that he must change his occupation if it is incompatible with the proper ulcer regimen. That this is impracticable in many instances is obvious. I have known such patients to carry rations of suitable food with them to work and try in every reasonable way to keep their ulcer symptoms under control, only to find that they could not. At rest, particularly in the hospital ward, they are fine, and all goes well, but almost as soon as they return to work, the symptoms reappear. The type I am referring to now is not the high pressure person who has too much nervous tension to work and keep his ulcer under control. The ordinary moderately calm worker at a simple job may have to take the attitude that if no cure can be offered, he must either devote his time to taking care of himself or disregard the consequences of his ulcer and continue his work as best he can.

Psychologic factors should be carefully taken into consideration. Often advice from this viewpoint will turn the tide and make it possible for some persons to master their ulcer situation and continue to be an economic unit of society. Certainly, the physician should not overlook

this possibility before accepting an ulcer as intractable to conservative measures. I can recall one suicide that might have been prevented if the psychologic factors had been properly evaluated.

Intellectual stamina is perhaps a vague term, but the lack of it in some patients with ulcer keeps all concerned unhappy. In this group is the patient who will not give up alcohol and tobacco. He will cheat on the type of food best for him and will drive himself at play or in business to an extent incompatible with an ulcer diathesis. Admittedly, some persons of this type are of sufficiently low intelligence by birth that they are not to be held entirely accountable. Under these circumstances the surgeon may with a clear conscience attempt to achieve a better physiologic and mechanical setup for the patient.

I am not so sanguine, however, about accepting for a hazardous operation a patient who knows his faults but will not correct them. I am not surprised that some of my medical colleagues feel that they cannot carry the distasteful problem of coddling such a patient to an extreme. The surgeon, on the other hand, does not look with any pleasure on accepting such a patient, since he knows that after operation there will be no help from the patient himself. The whole challenge is to the operation alone, which all realize has not been perfected to such a foolproof degree that cooperation from the patient is not essential.

OPERATIVE PROCEDURES

With the possible exception of cicatricial obstruction in aged patients, there is a definite consensus at the present time that operation for cure of duodenal ulcer means radical subtotal gastrectomy. This has come about through a long period of trial and error, during which every conceivable procedure of a less radical nature has been attempted. It is apparent now that one must remove a large proportion of the acid cells in the fundus as well as the acid-activating cells of the antrum to lower continuously the acid level in the remaining stomach segment. This has resulted in a higher percentage of patients with long respites from further ulceration than any of the more conservative operations. Strangely enough, as experience has been gained in this field, the mortality rate for the radical operation appears to be actually lower than the rates for many of the lesser procedures. Doubtless, this statement is open to criticism, since it is apparent that present day gastric surgical procedure is attended by a better understanding of the numerous factors of safety, an understanding that has come about through many channels.

In the minds of those interested in the subject, subtotal gastrectomy means the actual removal of not less than two thirds of the stomach. Wangensteen and associates[9] made some interesting measurements of

9. Wangensteen, O. H.; Varco, R. L.; Hay, L.; Walpole, S., and Trach, B.: Gastric Acidity Before and After Operative Procedure with Special Reference to the Role of the Pylorus and Antrum, Ann. Surg. **112**:626-667, 1940.

the actual square centimeters that constitute a subtotal resection. Various men have used the terms "more than one half," "two thirds," "three fourths" and "four fifths" of the stomach volume to indicate what is meant by adequate resection. There have been advocates of the shoemaker type of resection on the basis that the antrum and the lesser curvature were the important structures to eliminate. Others have felt that the lesser curvature was not important to remove but that the fundus should be almost completely eliminated.[10] Provided one removes sufficient of the acid glands and all of the acid-activating hormone area, one may have some leeway in the actual maneuver. There is considerable experimental and clinical evidence to indicate that removal of the greater part of the lesser curvature and as much of the fundus as can be removed with comfort leaves a situation less likely to be followed by subsequent ulceration.

Finsterer's [11] idea of leaving enough of the antrum for easy closure and proceeding with subtotal gastrectomy proximal to this region in order to avoid the difficult mobilization of the duodenum in certain cases of extensive ulceration has met with too much favor. This he called resection for exclusion and apparently indicated that removal of the antral mucosa was worth while, although this step in the procedure has often been overlooked.

Ogilvie [12] described a similar operation based on physiologic principles and recommended the preservation of the antrum in order to prevent anemia after partial gastrectomy. He [13] emphatically retracted his belief in this operation and reported nine jejunal ulcers in 22 patients on whom he had performed physiologic gastrectomy. I performed this operation on 5 patients with duodenal ulcer and 3 with gastric ulcer and have abandoned it because in 4 of the patients with duodenal ulcer and in 1 with gastric ulcer jejunal ulcer developed. In a fair number of cases I have practiced removal of the antral mucosa as suggested by Bancroft [14] when it seemed impracticable to resect beyond the ulcer site in the duodenum. It would appear that the results in this group of cases are going to be as good as those in cases in which complete

10. Connell, F. G.: Fundusectomy: A New Principle in the Treatment of Gastric or Duodenal Ulcer, Surg., Gynec. & Obst. **49**:696-701, 1929. Zollinger, R: Gastric Resection with Removal of the Fundus in the Treatment of Duodenal Ulcer, Surgery **8**:79-93, 1940.

11. Finsterer, H., and Cunha, F.: The Surgical Treatment of Duodenal Ulcer, Surg., Gynec. & Obst. **52**:1099-1114, 1931.

12. Ogilvie, W. H.: Physiology and the Surgeon, Edinburgh M. J. **43**:61-83, 1936.

13. Ogilvie, W. H.: The Approach to Gastric Surgery, Lancet **2**:235 and 295, 1938.

14. Bancroft, F. W.: Modification of Devine Operation for Pyloric Exclusion of Duodenal Ulcer, Am. J. Surg. **16**:223-230, 1932.

subtotal resection was done. I am aware that great care must be used in denuding the antrum of its mucosa; if care is not exercised, perforation of the thinned-out muscularis and serosa will take place. This remnant is also a delicate structure to invert, and care must be used to make an adequate closure. I have often been tempted to try Schrimger's [15] idea of suturing the two denuded surfaces together without infolding, but as yet I have not used it.

It is admitted that one can, with greater comfort, turn in an adequate segment of antrum that has not been denuded and also that morbidity is higher among those patients having either difficult closure of the duodenal stump or closure of a denuded antrum. McKittrick [16] therefore felt that it might be wiser to accept a two stage procedure and do resection for exclusion as a first stage. Six weeks later, after complete subsidence of all inflammatory reaction, an easy resection of the pyloric segment can be accomplished. I am convinced that for use in selected cases this idea has much to commend it. I have been impressed with the ease of removal of such a segment after the occurrence of jejunal ulcer following the von Eiselsberg [17] or the Devine [18] operation or Finsterer's resection for exclusion.

I have usually employed a left rectus muscle retraction incision. As a rule, this gives adequate exposure of the upper segment of the stomach and allows for easy anastomosis. However, it does handicap somewhat the proper management of the duodenal stump in some cases. When the stomach is high and in a transverse position or when the patient has a wide flare of the costal border, I prefer either an oblique or some other modification of a transverse incision. I begin by selecting a site on the greater curvature well to the left of the junction of the right and left gastroepiploic vessels. The radicals of these vessels supplying the fundus are interrupted along the greater curvature, thus preserving the main vessels and the blood supply to the great omentum. This first maneuver is carried down to the antrum. Then the vessels of the lesser curvature are secured as far proximal as is practical. The stomach is then divided between heavy crushing clamps and the distal segment is lifted up, exposing the attachments of the antrum to the pancreas and the middle colic vessels. The remaining dissection depends on the acuteness and the inflammatory extension of the ulcer. If the area

15. Schrimger, F. A. C.: A Technic for the Management of Gastrojejunal Ulcers With or Without Gastro Colic or Jejuno Colic Fistula, Ann. Surg. **104**: 594-600, 1936.

16. McKittrick, L. S.: Personal communications to the author.

17. von Eiselsberg, A.: Ueber Ausschaltung inoperabler Pylorusstricturen nebst Bemerkungen über die Jejunostomie, Arch. f. klin. Chir. **50**:919-939, 1895.

18. Devine, H. B.: Basic Principles and Supreme Difficulties in Gastric Surgery, Surg., Gynec. & Obst. **40**:1-16, 1925.

involved obviously extends to the region of the bile ducts and the great vessels to the liver, a modified exclusion operation is done. I have denuded this remaining distal segment of its mucosa, hoping that this would eliminate anastomotic ulcer. If one prefers to leave the antral mucosa under these circumstances, then a second operation at a later date must be planned to eliminate this segment. I have abandoned the policy of cutting across the duodenum at the upper border of an ulcer on the posterior wall and leaving the ulcer bed attached. Although one can get fair closure by suturing the anterior wall of the duodenum to the pancreas, in such cases there has been more trouble with leakage and abscess formation. I am convinced that if the duodenum is transected, this should be done in such a manner that at least 2 cm. of free bowel remains for an adequate turn in. This is possible with all quiescent ulcers, and most of these are sufficiently high to allow resection of the ulcer site, even if they are on the posterior wall. If the ulcer is on the descending limb of the duodenum, one can often find sufficient free intestine proximal to the ulcer but distal to the pyloric sphincter to make a satisfactory closure. I am convinced that actual removal of the ulcer itself is unimportant. Much help can be obtained by freeing the duodenum from its outer attachments as first described by Finney.[19] This exposes the course of the common bile duct so that one can easily determine the entry of the duct into the duodenum. Many adherent ulcers can be included in the resection if this precaution is carried out which on first inspection appears to be too extensive to permit mobilization and closure of the stump. The only risk one must accept in such a maneuver is that having freed the ulcer site too extensively to allow leaving it, one finds that actually it is too close to the papilla of Vater to allow adequate closure. This may be avoided in two ways. One way is not to disturb the ulcer itself but to use the modified exclusion procedure I have advised or accept a two stage operation. If, on the other hand, one only frees the outer attachments of the duodenum and looks over the situation, no harm results, and in many cases the ulcer is found to be well above the papilla of Vater.

Types of anastomosis between the stomach segment and the jejunum are varied; they are all modifications of the Billroth II idea. Some prefer closing the upper half or two thirds of the cut end of the stomach as suggested by Hofmeister[20] and utilizing the fundal segment for anastomosis. Finsterer expressed the opinion that by attaching the unopened proximal segment of the jejunum to the upper, turned-in portion of the stomach a better mechanical and physiologic stoma is

19. Finney, J. M. T.: A New Method of Pyloroplasty, Tr. Am. S. A. **20**:165, 1902.

20 Hofmeister, F., cited by Stumpf, R.: Beitrag zur Magenchirurgie, Beitr. z. klin. Chir. **59**:551, 1908.

produced. Graham, using a shoemaker clamp on the upper segment, obtained the same result but left more of the fundus than some believe to be safe. May [21] recently advocated a form of anastomosis that utilizes the entire cut surface of the stomach, but by puckering the stomach edge the resulting stoma is centrally placed and the lower margin elevated to prevent dumping. I have often been able to use the entire segment of the stomach by drawing the freed organ strongly toward the right; the structure is thus made tubelike before the clamps are applied. After anastomosis, when this is done, the stoma assumes an oblique or nearly transverse direction, which has given satisfactory results. I have seen no disabling symptoms from rapid emptying. If the stomach is large, I usually close the lesser curvature portion and utilize the fundal half in the anastomosis. By starting each row of sutures at the lesser curvature segment, one above the other, I accomplish much the same mechanical situation that Finsterer has advocated. I use two rows of fine chromicized catgut on atraumatic needles without silk reenforcement. Postoperative hemorrhage and leakage have not occurred in my cases.

There is considerable controversy regarding antecolic and retrocolic anastomosis. Lahey,[22] Rienhoff,[23] McClure [24] and others have preferred to use the antecolic route as a rule. They have found it easier to carry out; they have reported little trouble from the long proximal loop regurgitating large quantities of bile into the stomach when the patient lies down, and they like its accessibility if reoperation should become necessary. I have tested many patients with the idea of performing anterior anastomosis, only to find that often the jejunal mesentery was not long enough to permit an anterior hook-up to the high short stomach segment without tension. Actually, on some occasions when I felt it important to make an antecolic anastomosis, I have divided a heavy great omentum from its distal border to the colon in order to carry out the procedure. Occasionally, I have seen disturbing partial obstruction to the colon during the convalescence due, I believe, to the pressure of the jejunum on the large bowel while adjustments were taking place. One should never be tempted to use enteroenterostomy between the long loops of the jejunum when dealing with ulcer, although this will often simplify

21. May, H.: Reconstruction of the Stomach Outlet in Gastric Resection: Simple Suture for Use with the Billroth 2 Oralis Totalis Type of Operation, Arch. Surg. **44**:378 (Feb.) 1942.

22. Lahey, F. H., and Marshall, S. F.: Surgical Treatment of Peptic Ulcer Based upon One Hundred and Thirty Subtotal Gastrectomies for Peptic Ulcer, New England J. Med. **217**:933-940 (Dec. 9) 1937.

23. Rienhoff, W. F., Jr.: Sympathetic Nerve Block as an Adjunct Anesthesia in Minimal Resection of the Stomach for Peptic Ulcer, Ann. Surg. **110**:886-906, 1939.

24. McClure, R. D., and Fallis, L. S.: Partial Gastrectomy: A Consideration of Certain Technical Problems, Ann. Surg. **111**:743-758, 1940.

the convalescence after high resection for cancer. In the presence of acid, jejunal ulcer will follow enteroenterostomy in a high percentage of cases. Walters, Lewis and Lemon [25] emphasized this hazard in a recent publication and used this as an argument against antecolic anastomosis.

I prefer a short loop retrocolic anastomosis in the average virgin case of ulcer in which the patient has a thin mesocolon. I am careful to suture the rent in the mesocolon to the stomach segment above the anastomosis; the posterior row of these sutures is placed before the anastomosis is done. It is important to make the opening in the mesentery to the left of the mesenteric vessels, since if this detail is overlooked malfunction is more apt to occur. In a patient who has had a previous operation on the stomach, particularly posterior gastroenterostomy, I feel it unwise to place the new stoma through the traumatized mesocolon. Likewise, in a patient with a thick fatty mesentery and one with a short mesocolon, I prefer the antecolic route. The tendency for the small bowel to attach itself to traumatized fat causes many complications. When peritonealization of the mesentery or its edge cannot be carried out, the anastomosis should be made as far away from such an area as possible.

After-Care.—The after-care of patients subjected to this type of operation is most important. I leave a previously introduced Levine tube in the stomach until a satisfactory gastric balance is assured. Feedings are gradually increased, and great care is used not to force food by mouth. If the patient is hungry, his feedings will nearly always pass through the stoma. If he eats when he feels full or does not desire it, dilation of the stomach segment will take place and delay convalescence. In the patient on the borderline of starvation one may use the Abbott-Rawson tube; this keeps the stomach segment empty but allows feeding directly into the distal jejunal limb. In many cases I have provided concomitant jejunostomy for feeding. This is particularly important when the serum protein has had to be brought to operable levels by blood transfusion. Clute [26] recommended an almost routine use of concomitant jejunostomy. If all goes well, the average patient can take a maintenance diet by the third postoperative day. He may be out of bed by the twelfth day and be able to go home on the eighteenth. He is usually able to resume his ordinary occupation by the end of the third month. He should remain under observation and be advised to continue to observe a reasonable regimen indefinitely. I have been

25. Walters, W.; Lewis, E., and Lemon, R.: Primary Partial Gastrectomy (Polya Type) for Duodenal Ulcer: A Study of Results in Two Hundred and Twelve Cases, Surg., Gynec. & Obst. **71**:240-243 (Aug.) 1940.

26. Clute, H. M., and Bett, L. M.: Jejunostomy for Postoperative Feeding, Tr. South. S. A. **53**:295-307, 1940.

impressed by the freedom from symptoms, by the fact that the usual three meals a day are satisfying, and by the ability of patients of this type to carry their regular economic load.

COMPLICATIONS

After subtotal gastrectomy for duodenal ulcer, I have had two chief reasons to worry. One is that an improperly handled duodenal stump may cause fistula, abscess, peritonitis or subdiaphragmatic infection. Though it happens only rarely that a duodenal stump is improperly handled, it is of sufficient importance to warrant careful management of this part of the operation. I have already pointed out many of the pitfalls, but I reiterate that if adequate closure of free uninvolved duodenum cannot be done, then a modification of the exclusion idea should be used.

The other complication is that of malfunction of the stoma. This, to be sure, occurs infrequently, but when it does, it calls for proper management. Some anastomoses fail to work from the beginning, and others function well for a number of days and then become occluded. Doubtless there are several factors at work, although poor mechanics, infection with resulting adhesions and edema from hypoproteinemia cover most of them. I have seen so many patients spontaneously recover from obstruction that I believe the obstruction in such cases is on the basis of either temporary edema at the suture line or inadvertent, insidious acute dilatation of the proximal stomach segment. Both factors may well have played a role. On the basis that the complication may be temporary, one should keep the stomach decompressed and treat the patient expectantly for at least a week. Welch and I [27] have shown that in treating young patients it is safe to delay intervention for a longer interval than in treating the older patients. I have further demonstrated to my own satisfaction that if the mechanical procedure is correctly carried out at the original operation, one need not interfere with the anastomosis. Jejunostomy for feeding, if done in time, will invariably allow nature to correct the faults at work about the stoma. This may take as long as fifty days and test the endurance of the victim and the surgeon to the utmost. The only exception to this rule that I have encountered was in the case of a patient who had posterior anastomosis made to the right of the mesenteric vessels through a short mesocolon. This patient eventually required revision of the anastomosis before relief was complete.

Although there has been a good deal of worry in the past as to hemorrhage at the suture line, this has not been a frequent occurrence in recent years. I believe that the use of crushing clamps on the

27 Allen, A. W., and Welch, C. E.: Jejunostomy for the Relief of Malfunctioning Gastro-Enterostomy Stoma, Surgery **9**:163-182, 1941.

remaining stomach segment helps to eliminate bleeding. Also, one must use considerable care to secure and ligate separately active vessels during anastomosis. The care with which tension is maintained on the suture and the manner in which the sutures are introduced do much to eliminate this complication.

Leakage of a suture line is in the same category as hemorrhage. One rarely hears of it now, but precautionary measures are always to be taken into consideration. The usual rules of good gastrointestinal surgical procedure apply. One must approximate without tension the two serous surfaces of the structures to be anastomosed. It is important to turn the mucosal edges into the open viscus. I believe that this is best accomplished by an inside and an outside row of sutures, the former inverting the mucosa. I think it unwise to use a third row of catgut sutures since this is simply a foreign body which nature must absorb, and it thus offsets any good that may come from it. I have found no fault with two rows of continuous fine chromicized catgut—the size 0 or 00 being adequate, depending on the make. I have not found a row of interrupted silk to be of any advantage.

Infection is, to be sure, always uppermost in the mind. Some duodenal ulcers harbor a virulent organism, and in 2 cases in my experience this has proved disastrous. At the moment I feel that care in walling off the field of operation, the use of suction on the inlying Levine tube and the employment of a suction tip during operation constitute the most satisfactory safeguards. I have had too little experience with the preoperative use of sulfaguanidine (sulfanilylguanidine) to warrant any opinion as to its efficacy. Cultures taken at operation after its use have so far not been convincing as to its value. The use of sulfanilamide powder in and about the operative field may prove of great aid in eliminating uncontrollable infection, but much more experience is needed to evaluate this procedure completely. I admit that I use it in all cases in which gastrectomy is done for malignant disease and in many cases in which resection is performed for ulcer. Wangensteen [28] devised a clamp suitable for aseptic anastomosis between the jejunum and the stomach. The method will certainly have strong supporters for its use in gastric resection for infected lesions, particularly cancer.

Pulmonary complications of varying degrees following gastric operations are still a problem. I am inclined to believe that some of the efficacy of procaine hydrochloride in inducing anesthesia and splanchnic block is due to the effect of this anesthetic on the vagus nerves. Adams [29]

28. Wangensteen, O. H.: Aseptic Gastric Resection, Surg., Gynec. & Obst. **70**:59-70, 1940.

29. Adams, R.: Personal communications to the author.

called my attention to the importance of procaine hydrochloride block of the vagus nerves during operations on the lung. He expressed the opinion that the same principles apply to gastric operations and that if the vagi are well anesthetized before sectioning, there will be a marked diminution in postoperative atelectasis. Pneumonia is far less dangerous than before the days of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). There are patients in a depleted condition, however, who cannot withstand pneumonia and surgical trauma combined, even with use of the most exacting methods of postoperative care.

SUMMARY AND CONCLUSIONS

Duodenal ulcer is primarily a medical problem. Approximately 80 per cent of the patients with this lesion respond to conservative measures.

Complications of duodenal ulcer demand surgical treatment. These are acute perforation, massive hemorrhage, cicatricial obstruction and intractability.

For the treatment of acute perforation, simple closure of the perforation is all that is indicated. This must be combined with proper after-care.

Massive hemorrhage from duodenal ulcer demands immediate hospitalization. Patients under 45 years of age will spontaneously cease to bleed with conservative treatment. At a time of election after complete recovery, subtotal gastrectomy is advised. Patients over 45 years of age are likely to bleed to death in spite of the best conservative care possible. Their condition should be carefully evaluated on admission and radical operation undertaken on many of them within seventy-two hours after the onset of bleeding. If delay beyond this period of time has occurred, then continuation of conservative treatment is indicated. The aged patient will rarely, if ever, withstand radical operation after a week or more of repeated bursts of bleeding and starvation.

Posterior gastroenterostomy, pyloroplasty and gastroduodenostomy are indicated only in the presence of scar tissue obstruction in aged patients.

Surgical cure of duodenal ulcer can be brought about only by subtotal gastric resection. This means the elimination of all the acid-activating cells in the antrum and a large proportion of the acid cells in the fundus. The operative mortality from this procedure has been reduced to a level compatible with the results obtained.

GASTRIC ULCER, BENIGN OR MALIGNANT

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ROCHESTER, MINN.

The morphologic characteristics and the evolution of most gastric ulcers are frequently unpredictable, and hence, in my opinion, most chronic gastric ulcers should be removed surgically without too much delay. After making such a bald statement, I should like to emphasize the fact that some small benign gastric ulcers and occasionally large ones may respond in an amazing fashion to a course of nonsurgical treatment. On the other hand, although many chronic gastric ulcers may seem to respond temporarily to a medical regimen, recurrence of the ulceration is frequent. This recurrence may be a new ulcer or a continuation of the original ulceration which did not heal but merely seemed to, and the recurrent lesion may be even larger and of more rapid growth than the original lesion. During this period, even while the patient has been on more or less of a medical regimen, fairly frequently there has been partial and sometimes almost complete physical disability. Were these the only disadvantages of delay in surgical treatment, there probably would not be much objection to a routine course of medical treatment before the decision whether or not surgical procedure should be carried out. The indecision relative to whether an ulcerating lesion of the stomach is benign or malignant places great responsibility on those who recommend methods of treatment other than removal of the lesion.

Although for years roentgenologists have emphasized that they cannot distinguish between benign and malignant gastric ulcer in a definite proportion of cases (about 10 per cent in the experience of the Mayo Clinic [1]) and surgeons have called attention to the facts that a definite proportion of the patients operated on for cancer of the stomach had been reported by the roentgenologist to have gastric ulcer (also 10 per cent [2]) and that it is difficult and even impossible in many cases of ulcerating lesions of the stomach to distinguish grossly and by palpation between benign and carcinomatous ulcer, there are still some who believe that

From the Division of Surgery, the Mayo Clinic.

1. Gray, H. K.; Balfour, D. C., and Kirklin, B. R.: Cancer of the Stomach, Am. J. Cancer **22**:249-286 (Oct.) 1934.

2. Walters, W.; Gray, H. K., and Priestley, J. T.: Malignant Lesions of the Stomach: Importance of Early Treatment and End Results, J. A. M. A. **117**:1675-1681 (Nov. 15) 1941.

there is a triad of clinical findings and responses to nonsurgical treatment which is a criterion of benignancy. This triad consists of relief of symptoms, disappearance of the niche in the roentgenogram and disappearance of blood from the stools. If these three requirements are satisfied, it is assumed by some that the lesion has healed and hence was benign. The belief that this triad is indicative of healing or of benignancy has been shown to be erroneous by the frequently repeated reports of cases in which the triad was present but the lesions had not healed and were not benign.

In a symposium presented at the Ninety-Second Annual Session of the American Medical Association, June 6, 1941, Eusterman [3] concluded as follows:

> . . . It is apparent that gastric carcinoma not only may masquerade successfully as benign ulcer but may react to treatment in similar fashion as well.

In the discussion, Dr. Sara Jordan [4] stated

> . . . that neither the size of the ulcer nor the age of the patient nor the presence of normal acid or hyperchlorhydria should lessen our suspicion of carcinoma, for some of our largest lesions have been benign and some of the smallest malignant. and malignant lesions occur often enough in the young, and benign ulcers often enough in the middle aged and old, and acid is present often enough where the lesion is malignant, so that these three criteria of size of ulcer, age of patient and presence or absence of acid have no actual or practical value in the diagnosis of the individual patient.

Dr. Portis [5] made the following statement:

> . . . As I maintained years ago and still maintain, I would trust only the microscope in making this fine differential diagnosis. I still feel that gastric lesions, for the most part, are better handled by the surgeon. I am not discussing persons in their early twenties with a small, acute ulcer, but particularly that group of patients beyond 35 years of age who are good operative risks. I am convinced that the mortality and morbidity which would accrue in handling these early lesions surgically would be far less than a similar large series of cases handled medically.

I have chosen to quote extensively from this symposium because it gives the crystallized opinion of the internists who participated in that discussion, all of whom have passed through the stage in the latter part of the 1920's when practically all patients who had gastric ulcer were subjected routinely to medical treatment unless the lesion was large or

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3. Eusterman, G. B.: Carcinomatous Gastric Ulcer: Misleading Results of Medical Therapy, J. A. M. A. **118**:1-5 (Jan. 3) 1942.

4. Jordan, S. M., in discussion on papers of Eusterman [3] and Rafsky and Weingartner, J. A. M. A. **118**:10 (Jan. 3) 1942.

5. Portis, S. A., in discussion on papers of Eusterman [3] and Rafsky and Weingartner, J. A. M. A. **118**:10 (Jan. 3) 1942.

the patient's pain such that it was difficult to control by nonsurgical methods. At that time I was particularly disappointed in this nonsurgical trend in the treatment of ulcerating gastric lesions because I was operating repeatedly on patients with carcinoma, many of whom had been treated for months for a suspected benign ulcer of the stomach or the duodenum because of similar histories and effective temporary responses to nonsurgical treatment before the recognition that the lesion was carcinomatous. Unfortunately, when some of these patients were operated on, it was found that the malignant lesion was no longer suitable for removal. Then there was another group of cases in my experience in which there was chronic gastric ulcer which was thought to be benign. However, when operation was performed, the lesion was found on microscopic examination to be carcinomatous ulcer or ulcerating carcinoma rather than benign ulcer. There was another group which seemed by virtue of age, smallness of lesion or response to medical therapy to have benign ulcer that seemed on roentgen examination to disappear. The patient, feeling well, was allowed to go home only to return months later either with benign ulcer larger than the original or with ulcerating carcinoma.

Recently (Dec. 22, 1941), I operated on 2 patients whose history and clinical picture, as well as the report of the roentgen examination of the stomach and the pathologic nature of the lesion after its surgical removal, seem to me to emphasize, when studied in parallel, some of the problems in making the preoperative diagnosis of ulcerating gastric lesion, and yet the indications for surgical treatment were apparent.

The first patient was a man aged 54 years. The crater of the gastric ulcer had increased from 1 to 2.5 or 3 cm. in diameter over a period of eleven months (fig. 1). This man had received a course of medical treatment in a hospital while he was registered at the clinic and had been sent home with the prescription of a diet for ambulant patients with ulcer. His history of stomach trouble dated over a period of only three and a half years. In addition to the gastric ulcer noted on both roentgen examinations, a duodenal ulcer was observed. Analysis of the gastric contents revealed a total acidity of 78 and free hydrochloric acid of 66 (Töpfer's method). Partial gastrectomy was performed on Dec. 22, 1941. The report of the pathologist indicated that 15 cm. of the stomach and 3 cm. of the duodenum had been resected. The stomach contained a simple ulcer (3 by 2.5 by 1 cm.) with marked eosinophilic infiltration, and there was an ulcer also in the duodenum.

In this case the increase in the size of the ulcer was surprising in view of the fact that the patient had been placed on a medical regimen for the treatment of the ulcer when he first was seen at the clinic on Aug. 6, 1940. At this time a roentgenogram of his stomach showed "hypertrophic gastric mucosa, two very small areas of ulceration in the lesser curvature at the angle of the stomach which may be associated with gastritis and also duodenal ulcer." He was given medical

treatment in the hospital between August 14 and August 25. On August 22 a roentgenogram of the stomach was negative; a duodenal ulcer was present. The patient was seen again on Jan. 15, 1941; at that time the gastric ulcer was barely demonstrable by roentgenogram. He was maintained on a regimen for ambulant patients with ulcer.

Except for the duodenum the roentgenogram of the second patient was similar to that of the first patient. A large perforating gastric ulcer was reported but

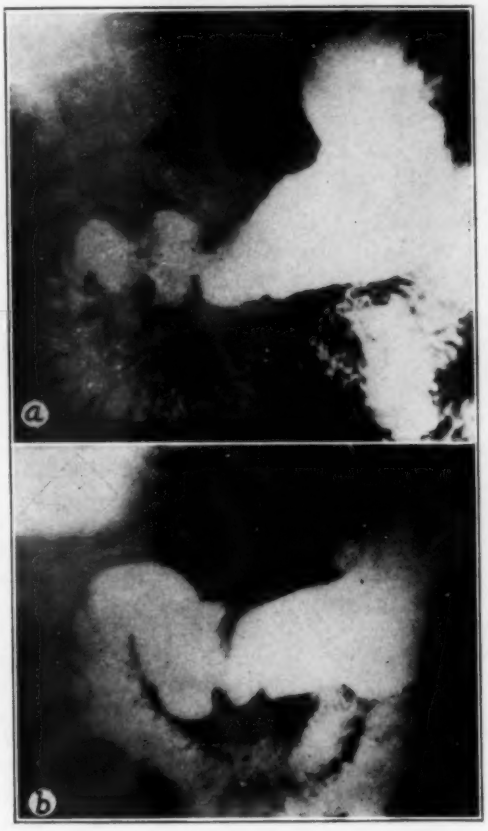

Fig. 1.—(*a*) Roentgenogram of the stomach taken Jan. 15, 1941, showing small gastric ulcer at the incisura; (*b*) roentgenogram of the stomach of the same patient, taken Dec. 18, 1941, showing large perforating gastric ulcer.

designated by the roentgenologist as probably malignant (fig. 2). This patient was 42 years of age and had had a history of stomach trouble for twenty years. Gastric acids varied from 40 to 18 and free hydrochloric acid from 10 to 0. Partial gastrectomy was performed on Dec. 22, 1941; at that time two thirds to three fourths of the stomach was removed. The pathologist reported that 15 cm. of the stomach was removed and contained an ulcerating and perforating grade 4

signet ring colloid adenocarcinoma (3 by 3 by 1 cm.) and that the carcinoma had extended through the gastric wall. No glandular involvement was observed. The striking feature in this case is that for a twenty year period the patient had a history of the type which I have referred to frequently as ulcer history; there had been no changes in that history in recent years, and still the lesion was found at operation to be grade 4 signet ring colloid carcinoma. One wonders what the lesion was that accounted for the patient's ulcer type of dyspepsia over such a long period and whether or not an ulcer preceded the formation of the ulcerating carcinoma.

Fig. 2.—Large perforating gastric lesion reported as gastric ulcer, probably malignant.

A critical analysis, however, of both these cases shows that a differential clinical diagnosis probably could have been made between the two lesions prior to operation, for the man who had carcinoma was reported to have a "gastric ulcer, probably malignant," by roentgen examination, and he had a low concentration of free hydrochloric acid on analysis of the gastric contents. Misleading, however, was his long history (twenty years) of ulcer dyspepsia. The patient who had the benign gastric ulcer had also a duodenal ulcer. However, the gastric ulcer increased in size under a regimen for ambulant patients with ulcer, and

the patient showed some symptoms of ulcer. In regard to the relation of gastric acids to benign and malignant gastric ulcer, Allen and Welch [6] showed that free hydrochloric acid is present in about the same proportion of cases of benign gastric ulcer as of "ulcer-cancer." In a study of a series of cases of carcinoma of the stomach Gray, Priestley and I [7] found that in approximately 50 per cent of the cases there was free hydrochloric acid, that in approximately 15 per cent the free hydrochloric acid values were more than 30 and that in 5 per cent they were more than 50.

Before leaving this discussion relative to the difficulty of distinguishing between some benign gastric ulcers and some carcinomatous ulcers, I should like to refer to a group of cases in which gastric ulceration, either benign or malignant, so interferes with the neuromuscular activity of the stomach that a marked degree of pylorospasm is set up and leads to the erroneous impression that the lesion is in the duodenum and is benign when in reality it is in the lesser curvature of the stomach and may be malignant. The presence of pylorospasm and barium sulfate in the lower part of the stomach may so mask the outline of the stomach that the presence of gastric ulceration may be overlooked entirely. I have reported from time to time several cases of this type.[8] In many of them a so-called ulcer type of dyspepsia has been present, sometimes for as long as eight or twelve years. In cases in which pathologic examination of the ulcerating lesion proved it to be grade 4 (Broders' method) and highly malignant, the death of the patient within a year or two after resection seemed to be clinical confirmation of the highly malignant nature of the lesion.

To emphasize again that these cases are not rare but occur rather frequently, I should like to give a brief abstract of the record of 1 patient, a physician, whose case can be included in this group.

The patient, a man 55 years of age, registered at the clinic on Aug. 12, 1937. At that time a diagnosis of hemorrhagic duodenal ulcer with obstruction was made. The patient desired to try a course of medical treatment before resorting to surgical treatment and therefore went home. He returned on December 9, when the roentgen report was duodenal ulcer with obstruction and marked pyloric deformity. I operated on him on December 16, performing partial gastrectomy. There was a grade 4 ulcerated adenocarcinoma (3 cm. in diameter) situated on the lesser

6. Allen, A. W., and Welch, C. E.: Gastric Ulcer: The Significance of This Diagnosis and Its Relationship to Cancer, Ann. Surg. **114**:498-506 (Oct.) 1941.

7. Walters, W.; Gray, H. K., and Priestley, J. T.: Malignant Lesions of the Stomach: Results of Treatment in the Years 1907 to 1938, Inclusive, Tr. West. S. A. **50**:200-218, 1940; Malignant Lesions of the Stomach: Results of Treatment in the Years 1907 to 1938 Inclusive, S. Clin. North America **21**:1099-1115 (Aug.) 1941; footnote 2.

8. Walters, W.: Carcinoma of the Stomach, Proc. Internat. Assemb. Inter-State Post-Grad. M. A. North America, 1937, pp. 86-91; Surgical Lesions of the Stomach and Duodenum, Texas State J. Med. **34**:521-530 (Dec.) 1938.

curvature of the stomach immediately proximal to the pylorus. No glandular involvement was found. The patient returned to the clinic on March 27, 1939. Examination revealed recurrence of carcinoma with hepatic and supraclavicular metastatic growths. There was secondary anemia. Roentgen examination at this time showed the anastomosis to be free. The liver was larger than it had been formerly.

The trained gastroscopist has been helpful in describing the appearance of the lesion in the stomach. Even with the lesion observable, the possibility of misinterpretation by the gastroscopist of the pathologic nature of the ulcerating lesion must be emphasized definitely as a possible source of error. In spite of this, gastroscopy has been an important and necessary adjunct to recognizing the presence of intragastric lesions and observing their progress when they are treated by nonsurgical methods.

Several weeks ago I sent a patient into the hospital for three weeks' trial of medical treatment. Roentgen examination revealed a gastric ulcer high on the lesser curvature of the stomach and a duodenal ulcer. After the patient had been in the hospital for a week, the ulcer symptoms completely disappeared, and tests for blood in the stools gave negative results. At the end of the third week the roentgen examination was reported as showing disappearance of the lesion, but gastroscopic examination showed a small ulcerating lesion still present. In other words, had a gastroscopic examination not been made, the erroneous impression might have been reached that the ulcer had healed.

On the other hand, I operated recently on a patient who was suspected at home of having a malignant lesion of the stomach; yet roentgen examination on two occasions at the clinic failed to reveal the presence of a gastric lesion. Gastroscopic examination, on the other hand, was reported to reveal an ulcerating lesion high on the posterior wall of the stomach just off the lesser curvature. At operation both extragastric and intragastric exploration under visual control showed only hypertrophic gastritis with some spotty grayish exudate here and there between the hypertrophied gastric rugae.

These cases are exceptions; yet in both the patients were observed during the course of one month. They indicate that one cannot always rely implicitly on the roentgenogram in determining the changing character of a gastric ulcer and likewise that the gastroscopist's interpretation of his findings is subject to the same possibility of error that human beings apparently must always contend with.

The seeming disappearance of the crater in the roentgenogram or the decrease in size of the crater when the gastric lesion is malignant has been seen by Schindler [9] to be due to the infiltration of the crater by the carcinomatous process originating in one edge of the ulcer, granulation tissue filling in the remainder. Eusterman [8] stated that Rigler and Mallory made similar observations.

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9. Schindler, R.: Early Diagnosis of Cancer of the Stomach: Gastroscopy and Gastric Biopsies, Gastrophotography, and X-Rays, J. Nat. Cancer Inst. **1**:451-472 (Feb.) 1941.

CAUSES OF DELAY OF SURGICAL TREATMENT

I think I have shown the fallacy of the idea that all patients who have chronic gastric ulcerating lesions should be given a trial of medical treatment. The reasons for my viewpoint are the difficulty of distinguishing between chronic gastric ulcer and carcinomatous ulcer and the frequency with which gastric ulcers recur after nonsurgical treatment. Further, the argument that the risk of removal of a gastric ulcer carries a higher mortality rate than the risk of the lesions being malignant is not borne out by the fact. Certainly, during the past ten years, in which progress in American surgery has had no equal, the risk of operative procedures by well trained surgeons has decreased to a remarkable degree. I believe that the risk of removal of a gastric ulcer is not in excess of 5 per cent and that it is possible to operate on a large series of patients who have gastric ulcer with a mortality rate considerably less than that. In point of fact, partial gastrectomy was performed at the Mayo Clinic [10] in 89 cases in 1939 with a mortality rate of 2.2 per cent and in 88 cases in 1940 [11] with but 1 death. In addition, excision of the ulcer, with or without gastroenterostomy, was performed in 17 cases of gastric ulcer with no deaths. Operation was performed on 64 per cent of the patients suffering from gastric ulcer seen at the clinic in 1939 and on 61 per cent in 1940.[12]

From the standpoint of the possibility of recurrence of the ulceration, I have never observed benign gastric ulcer to recur or gastrojejunal ulcer to develop when half or more of the stomach, including the ulcer, had been removed.

Another argument sometimes used to avoid surgical removal of the lesion is that the ulcer is located so high on the lesser curvature that it might not be removable or could be removed only with great risk. In August 1940,[13] I emphasized the point that gastric ulcers which appeared on roentgen examination to be located high on the lesser curvature were frequently not as inaccessible as they seemed to be, for at operation it was found that the perforation of the lesion into the capsule of the pancreas had so foreshortened the stomach above the lesion as to give an erroneous idea of the amount of stomach between

10. Priestley, J. T.; Gray, H. K., and Walters, W.: Report of Surgery of the Stomach and Duodenum, 1939, Proc. Staff Meet., Mayo Clin. **15**:707-717 (Nov. 6) 1940.

11. Gray, H. K.; Walters, W., and Priestley, J. T.: Report of Surgery of the Stomach and Duodenum for 1940, Proc. Staff Meet., Mayo Clin. **16**:721-727 (Nov. 12) 1941.

12. It may be interesting to compare the operability rate for gastric ulcer with that for duodenal ulcer. In 1939 at the clinic 18 per cent of the patients who had duodenal ulcer were operated on, and in 1940, 15 per cent.

13. Walters, W.: Cardial Gastric Ulcers: Results of Operation for Apparently Inaccessible Lesions, Arch. Surg. **41**:542-553 (Aug.) 1940.

the ulcer and the esophagus. In these cases there was actually more uninvolved stomach than the roentgenogram indicated. The early division of the gastrohepatic omentum at a high level assists in mobilizing the upper part of the stomach so that unusually high lesions can be removed without too great difficulty, especially when the original method of Billroth or the Hofmeister modification of the Polya operation is used, in which a greater portion of the lesser curvature (containing the ulcer) than of the body or the greater curvature is removed.

At that time Cleveland and I [13] had studied a group of consecutive cases of cardial [14] lesions in which operation had been performed during 1938 and 1939 at the clinic. Thirty-five of these patients with cardial benign gastric ulcers were operated on. Partial gastrectomy was done in 26 cases with 1 death, a mortality rate of 3.8 per cent. In 4 cases the ulcer was excised, and gastroenterostomy was performed. In 1 case excision of the ulcer alone was done, and in 4 cases gastroenterostomy was performed. In these 9 cases there were no deaths.

Personally, I believe that the ulcer can and should be removed in every case, even though it may be located so high on the lesser curvature of the stomach that it has to be removed by cautery puncture, or, if it is high on the posterior wall of the stomach, that transgastric excision is necessary.

Finsterer [15] and Rieder [16] have advocated the Kelling-Madlener type of subtotal gastrectomy which allows the ulcer to remain in situ when it is situated too high to be removed with safety. Lewisohn [17] stated that he does not favor the Madlener procedure, for the postoperative results, when viewed in large numbers, are unsatisfactory. In my experience, in many of these cases the benign ulcer has healed after gastroenterostomy as reported by Eusterman and Balfour.[18] The probable explanation of the healing of such an ulcer is the relative achlorhydria which occurs in such cases as the result of the gastroenterostomy from dilution and neutralization of gastric acids accomplished by reflux of biliary, pancreatic and duodenal secretion into the stomach through the gastroenteric stoma.

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14. In this paper the adjective "cardial" is used in reference to the cardia, in contradistinction to "cardiac," which is generally used in reference to the heart.

15. Finsterer, H.: Das cardianahe Magengeschwür, Wien. klin. Wchnschr. **52**:394-400 (April 28) 1939.

16. Rieder, W.: Chirurgische Behandlung des kardianahen Ulcus ventriculi, Arch. f. klin. Chir. **196**:640-655, 1939; abstracted, Internat. S. Digest. **29**:21-22 (Jan.) 1940.

17. Lewisohn, R.: Problems in the Surgical Treatment of Chronic Duodenal Ulcers, Ann. Surg. **111**:355-361 (March) 1940.

18. Eusterman, G. B., and Balfour, D. C.: The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1935, p. 259.

Personally, I have found the procedure of choice to be subtotal gastrectomy going well beyond the lesion and removing it. The advantages of this procedure are the removal of the lesion with its possibilities of hemorrhage, perforation or malignant degeneration, riddance of associated pylorospasm and decrease in the quantity and concentration of gastric acid secreted and stimulated, resulting in almost constant incidence of relative achlorhydria with almost total absence of gastrojejunal ulceration. The Polya type of end to side anastomosis posterior to the colon without enteroanastomosis is, in my opinion, perferable to anterior anastomosis. The Billroth I (Haberer) method of direct anastomosis as modified by Horsley and Haberer is used occasionally in selected cases.

The Billroth I type of anastomosis after partial gastrectomy is a satisfactory treatment of gastric ulcer and carcinoma in selected cases. It is particularly useful in instances in which the duodenum is mobile and the lesion is in the lower third or half of the stomach, for, under these circumstances, end to end anastomosis can be made without tension on the suture line. Clagett and I [19] noted in a study of 272 consecutive operations for gastric ulcer performed at the clinic that this procedure was used 22 times in contrast to the posterior Polya operation, which was used 131 times. It should be emphasized that the results of the Billroth I procedure for gastric ulcer are satisfactory in a much higher precentage of cases than those of operations of a similar type for duodenal ulcer. This is probably due to the fact that the Billroth I operation produces a relatively high incidence of postoperative achlorhydria in cases of gastric ulcer and does not in cases of duodenal ulcer.

When the condition of the patient is such that removal of the lesion as a part of subtotal gastrectomy cannot be done without too great risk, then as safe a procedure as possible should be utilized which sufficiently reduces gastric acidity and reduces gastrospasm so that healing of ulceration may be anticipated. Surprisingly good results may be obtained by less radical methods, such as excision of the ulcer or cautery puncture with gastroenterostomy as advised by Balfour [18] or occasionally by excision of the ulcer alone. Protection against further ulceration is accomplished by reduction of acidity by the gastroenterostomy. This was done 50 times with good results in the series of cases studied by Clagett and me. Eusterman and Balfour [18] showed that 79 per cent of 100 patients on whom gastroenterostomy had been performed for gastric ulcer were well after five years. This procedure of low risk (3.9 per cent for 540 cases according to Eusterman and Balfour) is thus worthy of consideration when conditions make removal impossible. The

19. Walters, W., and Clagett, O. T.: The Surgical Treatment of Chronic Gastric Ulcer: Review of Two Hundred and Seventy-Two Cases, Surg., Gynec. & Obst. **71**:75-79 (July) 1940.

palliative resection of Madlener, in which also the ulcer is left behind, has not been utilized at the clinic.

Excision with knife or cautery may be done occasionally without gastroenterostomy, but it is not recommended because it does not offer an alteration of gastric physiologic conditions to prevent recurrence.[20] In an occasional case it has been utilized with good results. It does enable microscopic study of the lesion.

Similarly, segmental or sleeve resection may be done to remove the lesion, but disturbance of gastric peristalsis may follow in its wake, even to the extent of the development of an hourglass deformity due to contracture of the anastomosis. In addition, little change of gastric physiologic conditions is produced, and recurrent ulceration may occur. Segmental resection has been used with some success in selected cases, however, but not in recent years, and it is not to be recommended.

SUMMARY

The morphologic character and the evolution of gastric ulcer are frequently unquestionable. In 10 per cent of the cases, gastric ulcer is malignant. In many cases of chronic gastric ulcer, healing is temporary under nonsurgical methods of treatment, and recurrence of the ulceration is frequent.

In cases of ulcerating gastric lesions in which the patients are put on a medical regimen, gastroscopic examination should be used as an adjunct to roentgen examination to determine the effect of the nonsurgical regimen on the ulcer.

Clinical experience has shown that gastric carcinoma not only may masquerade successfully as benign ulcer but may react to nonsurgical treatment in similar fashion to benign ulcer as well. The clinical symptoms thought to be pathognomonic of benign gastric and duodenal ulcer have occurred in a third of the cases of carcinoma in which operation was performed at the Mayo Clinic, and in 80 per cent of this group there has been temporary effective response to a medical regimen.

Proper surgical treatment directed toward removal of gastric ulcer has been followed by excellent results. In my experience no recurrences have taken place when the surgical method of removing half of the stomach including the ulcer was employed, and in my experience this is the procedure of choice, although in an occasional case in which the ulcer is located high on the lesser curvature or the posterior wall, excision of the ulcer with gastroenterostomy has been followed by excellent results.

The operative risk in the removal of gastric ulcer should not exceed 5 per cent. In the hands of experienced surgeons the risk of partial gastrectomy with the removal of such lesions should not exceed 3 or 4 per cent.

20. Reduction of gastric acidity and relief of pylorospasm.

VITALLIUM CUP ARTHROPLASTY OF THE HIP

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When Venable, Stuck and Beach [1] introduced vitallium for use in orthopedic surgical procedures, this nonelectrolytic alloy was immediately employed in many forms. One of these was a cup to be used in arthroplasty of the hip joint.[2] In January 1939, Smith-Petersen [3] reported the results of fifteen years of experimenting with mold arthroplasties and gave a preliminary report on the use of the vitallium cup as an interposing substance in arthroplasty of the hip. In his report he outlined the details of his approach to the hip joint and emphasized the importance of meticulous operation and the necessity for anatomic restoration of the hip joint. Since June 1939, twenty vitallium cup arthroplasties have been performed on 17 patients at Duke Hospital. Eighteen of these operations, with a follow-up period of from eight months to two years, are included in this preliminary report. One patient has not returned for follow-up examination, and another was operated on too late for his case to be included in this paper.

Before the results of the operations to be reported are analyzed, the conclusions reached by previous workers in this field of surgery should be reviewed. A variety of absorbable and nonabsorbable materials have been used as interposing substances for arthroplastic procedures. Plates of silver, magnesium, aluminum, gutta-percha and celluloid were first used; later animal membranes, such as pig bladder and the walls of ovarian cysts, were introduced as joint linings. Though muscle flaps and periosteal

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Read before the Section on Orthopedic Surgery at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 4, 1941.

1. Venable, C. S.; Stuck, W. G., and Beach, A.: The Effects on Bone of the Presence of Metals, Based upon Electrolysis: An Experimental Study, Ann. Surg. **105**:917, 1937.

2. Hopkins, H. H., and Zuck, F. N.: Arthroplasty of the Hip, with Use of Vitallium Cup, M. Bull. Vet. Admin. **15**:1, 1938.

3. Smith-Petersen, M. N.: Arthroplasty of the Hip, J. Bone & Joint Surg. **21**: 269, 1939.

flaps were inserted with only fair success, John B. Murphy [4] developed the fascia flap method, which has served as a satisfactory basis for most of the modern arthroplastic procedures. Baer,[5] Campbell,[6] Putti,[7] the MacAuslands [8] and others outlined the various contraindications to arthroplasty and established standards by which to select cases and judge end results. In the selection of cases it was pointed out that the patient's general health must be good and his mental condition satisfactory for cooperation in a long and difficult convalescence. Putti stated, "We must therefore be prudent in proposing arthroplasty to a patient if we cannot thoroughly rely on his firmness of will to endure calmly the inevitable suffering and on his tenacious perseverance in the post-operative treatment." In addition to the patient's health, both physical and mental, his occupation and his ability to finance or to arrange for the financing of a long hospitalization must be considered.

Arthroplasty has been more successful in the presence of well preserved musculature, and better results have been reported from the treatment of bony ankylosis than from the treatment of fibrous ankylosis. It has been agreed that more effective results may be anticipated in the treatment of post-traumatic arthritis and of ankylosis following gonococcic infection. Arthroplasty for ankylosis following acute pyogenic infection has been found to be satisfactory provided that the disease process is completely quiescent and that eburnation or atrophy have not too greatly altered the bony structures adjacent to the joint. Albee [9] pointed out the difficulties encountered in cases which show decrease in the abduction leverage because of shortening of the neck of the femur. Campbell,[10] in outlining under fourteen headings the indications and contraindications for arthroplasty, counseled against using the procedure in cases of tuberculosis, emphasized the surgical maxim that all evidence

4. Murphy, J. B.: Arthroplasty, Ann. Surg. **57**:593, 1913.

5. Baer, W. S.: (*a*) Arthroplasty with the Aid of Animal Membrane, Am. J. Orthop. Surg. **16**:94, 1918; (*b*) Arthroplasty of the Hip, J. Bone & Joint Surg. **8**:769, 1926.

6. Campbell, W. C.: Arthroplasty of the Hip, Surg., Gynec. & Obst. **43**:9, 1926.

7. Putti, V.: Arthroplasty, J. Orthop. Surg. **3**:419, 1921.

8. MacAusland, W. R., and MacAusland, A. R.: The Mobilization of Ankylosed Joints by Arthroplasty, Philadelphia, Lea & Febiger, 1929.

9. Albee, F. H.: Original Features of Arthroplasty of the Hip and Knee, J. A. M. A. **101**:1694 (Nov. 25) 1933.

10. Campbell, W. C.: Operative Orthopedics, St. Louis, C. V. Mosby Company, 1939.

of acute infection must have subsided at least one year before operation and warned against the pitfalls to be expected in attempts at arthroplasty in joints affected by progressive arthritis.

Well aware of these definite contraindications and warnings, we attempted twenty arthroplasties on patients with the following types of arthritis: atrophic (4 cases: in 1 quiescent and in 3 active); Marie-Strümpell (8 cases: in 4 quiescent and in 4 active); pyogenic (4 cases); gonococcic (2 cases), and post-traumatic (2 cases). In classifying the results in these cases two methods have been used. The first of these is based on definite functional requirements and sets as the minimum for a good end result a painless stable hip with good weight-bearing alinement and at least 25 degrees of active flexion. The second classification is based on a comparison of the patient's condition before and after the operation. We feel that the comparative analysis of the individual case is the more important, since several of the cases in which we obtained our most satisfactory results have been placed under the poor results group according to the first method of classification. In analyzing the results of treating the badly crippled patient, it is important to consider whether the bedridden patient has been made ambulatory. If the patient was ambulatory before the operation, has his gait been improved, and has his pain been lessened? Can he sit more comfortably and with better cosmetic result? Does he walk with less support? Is he satisfied, and would he go through the same operation and long postoperative treatment for the same result? If these questions can be answered in the affirmative, the operation has been of value, even though the desired basic standard for a good result has not been met in every detail—"the result to the individual is the test."

REPORT OF CASES

CASE 1.—A young man 20 years of age had pyarthrosis, followed by fibrous ankylosis and 30 degrees' flexion deformity of nine years' duration. A Venable type cup was used for arthroplasty. His condition was satisfactory at discharge on the thirty-sixth postoperative day. He failed to report for follow-up treatment or examination until twenty-one months later. There was no motion, and he had 35 degrees' flexion and 10 degrees' adduction deformity. The result was poor.

CASE 2.—A 24 year old woman was bedridden with bilateral pyarthrosis of the hips of five years' duration. There were bony ankylosis on the right side and fibrous ankylosis on the left side without deformities. The muscle tone was poor, and there was bilateral genu recurvatum with instability. When last examined (the left hip twenty months, and the right hip fourteen months, after operation) both hips had active flexion of 25 degrees and were painless and stable. The result was good.

CASE 3.—An 18 year old woman had gonococcic arthritis of five years' duration. There were bony ankylosis and a 45 degree flexion-adduction deformity. A Venable cup arthroplasty was performed. Subcutaneous adductor tenotomy was performed at the time arthroplasty was done. The early postoperative course was uneventful. There were pain and elevation of temperature on the nineteenth postoperative day; subsequently, spontaneous drainage occurred. When cultured the drainage material yielded a growth of Staphylococcus aureus; inoculations into guinea pigs gave negative results. Continuous drainage was maintained. There was recurrence of the deformity. The cup was removed in March 1941, twenty-one months after arthroplasty; the articular surfaces were covered by smooth fibrous tissue. The result was poor.

CASE 4.—A man 22 years of age suffered from gonococcic arthritis of three years' duration. There were fibrous ankylosis, marked bony proliferation and a

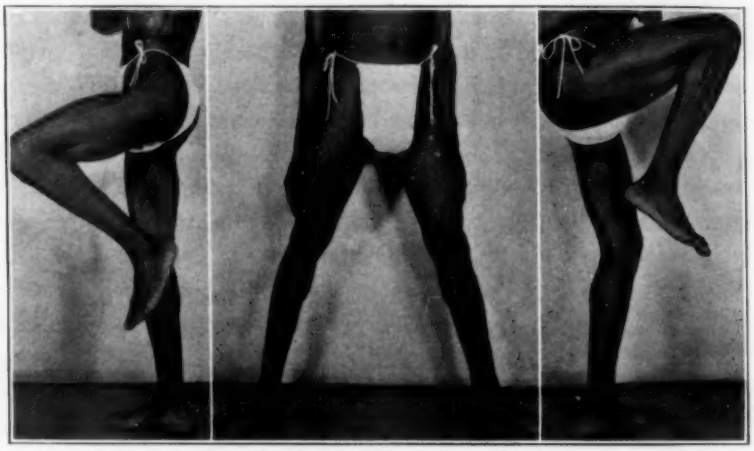

Fig. 1.—Photographs of the patient in case 4 twenty-one months after operation, showing the range of active flexion and the stability of weight bearing. The result was good.

45 degree flexion deformity. On examination twenty-one months after operation, the result was found to be good (fig. 1).

CASE 5.—A man 26 years of age had traumatic arthritis after fracture of the femur. The condition had endured for seven years. There was fibrous ankylosis in 10 degrees' adduction and the knee was ankylosed. A Venable cup arthroplasty was performed. Twenty-four months after operation there was no motion, and there was a 35 degree flexion and 25 degree adduction deformity. The result was poor.

CASE 6.—A man 37 years of age had a slipped epiphysis with traumatic arthritis of twenty-five years' duration. The head of the femur was large and flat; the acetabulum was shallow, and there was no deformity. There was a history of alcoholism; delirium tremens occurred on the third postoperative day. The opera-

tive wound disrupted, and there occurred self contamination with subsequent infection. Drainage was maintained for ten weeks. Twelve months after operation there were 20 degrees of motion and a stable hip. The result was poor (fig. 2).

CASE 7.—A man 23 years of age had active Marie-Strümpell arthritis of twelve years' duration with involvement of the hips and the knees of four years' duration. There was bony ankylosis on the right side in 10 degrees' flexion and 20 degrees' adduction; there was fibrous ankylosis on the left side in 20 degrees' flexion and 30 degrees' abduction. The spine was ankylosed. The general musculature was poor. Arthroplasty was performed. A Venable cup was used in the right hip and a Smith-Petersen cup in the left. When the patient was last examined (the right hip twenty-two months, and the left seventeen months, after operation), there was no motion or deformity. The result was poor.

Fig. 2.—Roentgenogram of the patient in case 6 one year after arthroplasty, showing bony proliferation about the cup. The patient had a postoperative infection, and drainage was maintained for ten weeks. There was marked fibrosis in the soft parts, which resulted in 20 degrees flexion deformity. At the time of writing the hip is painless and has 20 degrees of motion; there is a gluteal gait. The result was classed as poor, but the patient is showing gradual improvement.

CASE 8.—A man 25 years of age had active Marie-Strümpell arthritis of seven years' duration. There was fibrous ankylosis in 45 degrees' flexion. The entire spine was ankylosed and the motion in the opposite hip was limited. There were pain and limitation of motion in the hip not subjected to operation. Seventeen months after operation there was 30 degrees of active flexion; the hip was stable, and there was no deformity. The result was good.

CASE 9.—A man 28 years of age had inactive Marie-Strümpell arthritis of six years' duration. There was fibrous ankylosis in 45 degree flexion and 15 degree

abduction. The spine was solidly ankylosed. Subcutaneous adductor tenotomy was performed at the time arthroplasty was done. Cellulitis at the site of tenotomy appeared seven weeks after operation without complication. Seven months after operation there were 25 degrees of active flexion and slight pain. The result was fair.

Case 10.—A man 29 years of age was bedridden with inactive Marie-Strümpell arthritis of three years' duration. There was bony ankylosis in both hips; in the right hip there was 25 degrees' flexion and 10 degrees' adduction. The spine was solidly ankylosed. In the left femur there was old fracture with 3 inches (7.6 cm.) shortening; in the knee there was 10 degrees' motion. The musculature was poor. Thirteen months after operation the patient wished operation on the opposite hip; there was 40 degrees' flexion, and the hip was stable and painless. The result was good.

Fig. 3.—Roentgenogram of the patient in case 11 taken fourteen months after operation, showing ankylosis of the sacroiliac joints and the lumbar spine. At the time of writing restoration of the hip joint is satisfactory; the patient has 90 degrees of active flexion, walks with a stable hip and has no pain.

Case 11.—The patient was a man 30 years of age with active Marie-Strümpell arthritis of fifteen years' duration. There had been involvement of the hip for five years; there was fibrous ankylosis in 40 degrees' flexion and 20 degrees' abduction. The entire spine was ankylosed. Fourteen months after operation there was 90 degrees' flexion, and the hip was painless and stable. The result was good (fig. 3).

Case 12.—A man 34 years of age had inactive Marie-Strümpell arthritis of twelve years' duration. Fascial arthroplasty had been done on the right side. There was fibrous ankylosis on the left side. A Venable cup arthroplasty was done on the left side. A rubber drain was used for forty-eight hours. Postoperative infection occurred on the third day. The cup was removed six months after opera-

tion; the articular surfaces were covered by smooth fibrous tissue. In the right hip (the one on which fascial arthroplasty had been done) thirty-two months after operation there were 45 degrees' passive flexion and 15 degrees passive abduction with crepitus and pain. In the left hip twenty-two months after operation there were 35 degrees' passive flexion and 10 degrees' passive abduction with pain; the hip still continued to drain. Roentgenograms showed good joint space. The result was poor.

CASE 13.—A woman 31 years of age had inactive atrophic arthritis of fifteen years' duration. Fascial arthroplasty was done on the right side in 1932. There was fibrous ankylosis on the left side with 30 degrees' flexion deformity. The

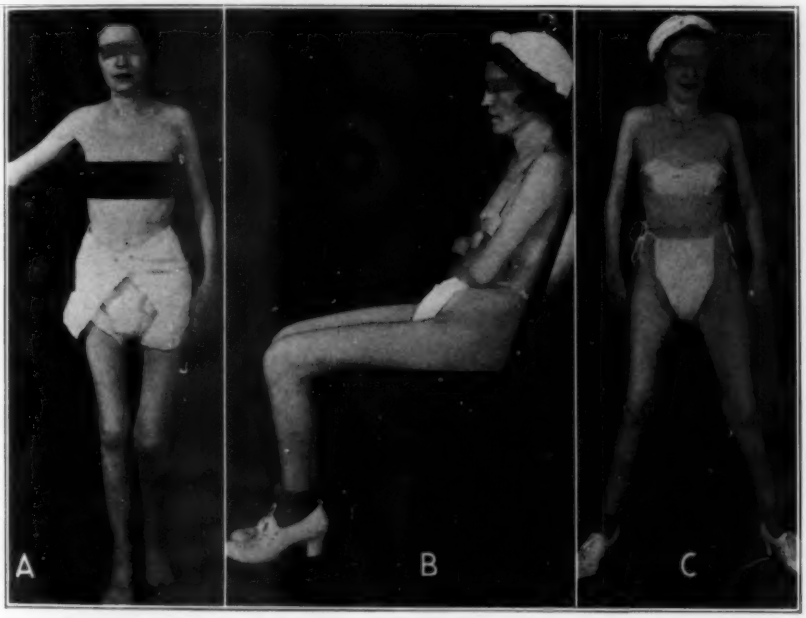

Fig. 4.—*A*, photograph of the patient in case 13 seven years after fascial arthroplasty of the right hip, showing flexion and adduction deformity of the left hip. *B* and *C*, photographs taken eighteen months after vitallium cup arthroplasty of the left hip. At the time of writing the patient walks without support with some bilateral gluteal gait. Note the arthritic changes in the hands.

spine was ankylosed. All peripheral points were involved. When examination was made eighteen months after operation on the right side, the result was good (fig. 4).

CASE 14.—A woman 39 years of age was confined to a wheel chair with active atrophic arthritis of fifteen years' duration. The hips had been involved for five years. In the right hip there were fibrous ankylosis, mild flexion and adduction deformity and poor musculature. Subcutaneous adductor tenotomy was per-

formed at the time arthroplasty was done. Fourteen months after operation there was 35 degrees' active flexion, and the hip was painless and stable. The result was good.

CASE 15.—A 40 year old woman had been bedridden for one year. She had active atrophic arthritis of six years' duration and bilateral fibrous ankylosis of the hips without deformity. The spine was ankylosed, and the knees were painful. Convalescence after the first arthroplasty (done on the left side) was complicated by generalized exacerbation of the arthritic process without involvement of the hip on which operation had been performed. When last examined (the left hip eighteen months, and the right hip eleven months, after operation) the patient's arthritis was active; there was generalized joint pain, and the hips were least symptomatic but painful. The result was fair (fig. 5).

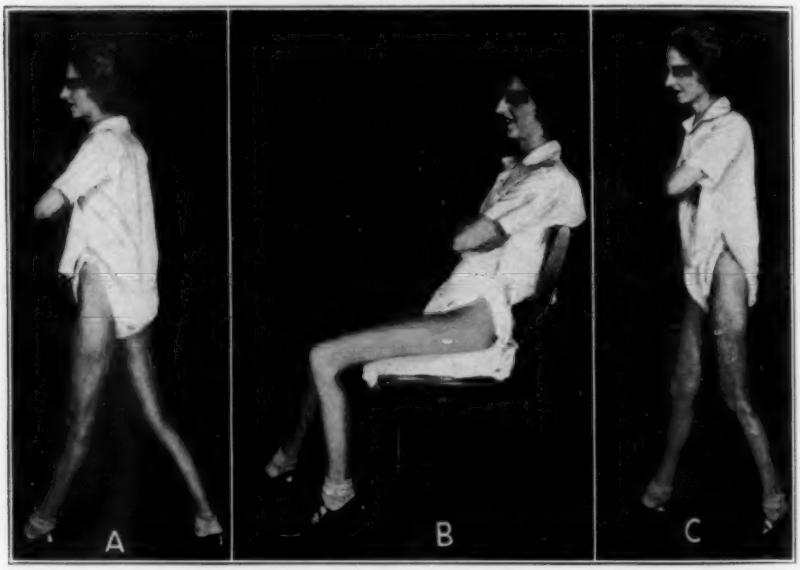

Fig. 5.—Photographs of the patient in case 15, who was bedridden with active atrophic arthritis one year before the first operation, showing the good range of motion eleven and eighteen months, respectively, after bilateral cup arthroplasties. There has been improvement in the general condition; the result was classified as poor because of pain, although the pain in the hips is not as marked as in the other joints.

COMMENT

In considering postoperative complications we have noted, as did Gill,[11] that any persistent postoperative limp, disability or deformity appears to be due largely to adduction and flexion of the thigh associated with insufficient mobility. Fibrosis about the site of operation resulting in contractures in the soft tissues has caused us a great deal of concern, and it has been most difficult, even with traction, to prevent flexion-

11. Gill, B., in discussion on Baer.[5b]

adduction deformities. After our most recent operation we used a plaster spica on the opposite extremity in an effort to control the pelvis and maintain adequate abduction and extension in the hip on which operation was performed. Adjustable posterior plaster sleeping shells in which the adduction can be controlled have been a part of the routine treatment.

In 1 patient in whom infection was present, calcification in the soft parts resulted in marked bony proliferation (fig. 2). Because of too short a femoral neck or possibly as a result of postoperative absorption of the neck, 2 patients had a bony bridge form across the new joint line. The cup was removed in 2 cases because of infection; in both instances the head of the femur and the acetabulum presented smooth glistening surfaces.

SUMMARY AND CONCLUSIONS

Our series of cases is too small to warrant any definite conclusions. Our impressions are these:

Too much emphasis cannot be placed on the necessity for meticulous operation and the importance of anatomic restoration of the hip joint.

There must be an adequate period of hospitalization and intelligent cooperation in the after-treatment.

Because of weakness of the gluteus medius muscle, inability to maintain abduction during weight bearing is a frequent postoperative complication.

Fibrosis is likely to occur in the soft parts, with resultant deformity and loss of motion.

It is difficult to predict an end result on the basis of the causation of ankylosis. Of the eighteen operations, eleven were on joints affected by atrophic arthritis or Marie-Strümpell disease. In this group the results of five were good, of three fair, and of three poor (the results of one were poor because of infection). On the pyogenic, the traumatic and the gonococcic joints, there were seven operations. The results of three were good and of four poor (the results of two were poor because of infection).

There has been no indication of any tissue reaction to the cup, and, in those hips for which arthroplasty is indicated, vitallium is a satisfactory interposing substance.

The operation is of particular value for bedridden and badly crippled patients.

Dr. R. Beverly Raney assisted in the clinical work on which this paper is based.

ABSTRACT OF DISCUSSION

Dr. Marius N. Smith-Petersen, Boston: The principle of this procedure is to insert an impermeable mold in which nature can do its repair work. It was originally intended that this mold be removed; this would leave two benign congruous surfaces, mechanically able to perform the functions of a normal joint. If physiologic repair is expected, physiologic conditions must be created. Fascia

lata arthroplasty did not succeed in bringing this about; a mechanically imperfect joint was created which might function satisfactorily for a time, but it seldom survived for long.

The mold arthroplasty is an attempt to imitate nature's original normal joint. A movable joint is created; in that joint the head of the femur moves inside the mold, and the mold moves inside the acetabulum. This must be kept in mind at the time of operation. The operation does not simply consist of slipping a mold over a partially molded head; the head must be smoothly finished, and the cup must fit the head, so that there will be an excursion of motion between the head and the mold. When the surgeon thinks that he has finished the operation, time and again he will find that his operative time will be lengthened because on testing the motion of the joint he finds that the motion is not as it ought to be: The cup may get caught in the acetabulum; there may be a little projection in the acetabulum that should be removed. There may be no motion between the head and the mold because of imperfect molding of the head. If the surgeon meets such conditions, he must not feel that he has been operating for a long time already and so must hurry; he must not say, "I guess I will let well enough alone."

If he makes his approach correctly, following structural planes with a minimum amount of bleeding, the patient should not be in shock by the time the hip joint is exposed. This is the time when the operator must be careful and slow in creating really congruous and mechanically perfect joint surfaces. Attention must be paid to the acetabulum as well as to the head; if the acetabulum is imperfect, the joint cannot be expected to function well. I am sure that in my earlier cases I did not pay enough attention to the acetabulum; I did not remove enough bone to make the cup freely movable in the acetabulum.

This operation is extensive and difficult. Every surgeon who contemplates doing it should practice on cadavers and see other surgeons who have had experience with it before he undertakes it.

The postoperative treatment is prolonged; much patience is required of both the surgeon and the patient. The surgeon should be sure to inform the patient beforehand that this procedure does not mean that he merely has to submit to an operation and then be handed a new joint on a silver platter. It demands cooperation between the surgeon and the patient if good results are to be obtained.

Dr. Baker stated that a stable hip with 25 degrees of motion is a good result. There must be more than 25 degrees of motion, even though the hip is stable; 25 degrees of motion means interference and impingement and, consequently, pain.

Dr. G. Mosser Taylor, Los Angeles: I wish to discuss another use for the vitallium cup. Mention has been made of the use of the vitallium cup in reconstruction operations for hip joints. I have 2 cases to present in which Whitman reconstruction of the hip joint was done with the use of the vitallium cup. In the past the biggest objection to reconstruction operations has been the pain. As far as stability of the hip is concerned this operation is satisfactory, but the persistent postoperative pain has left much to be desired. For this reason, the vitallium cup was tried.

In the first case, four procedures were done. First, a Whitman cast was used. After three months internal fixation was done. A year later a Bracket operation was attempted, but it failed. About the only thing left to do then was to fuse or to remove the head of the femur and insert a vitallium cup. The cup fitted over what was left of the neck of the femur without further reconstruction. The result has been at least fair. The hip is stable, furnishes efficient weight bearing and gives the patient little discomfort. There are flexion of 90 degrees and flexion

contracture of 20 degrees; there is abduction of 10 degrees. There is no adduction, but there is rotation of 10 degrees, with, however, a shortening of 1½ inches (3.8 cm.). Power in this case is not good. The patient is unable to balance herself on this leg. However, she does all her housework, and is well satisfied with the results.

In the second case reconstruction was done seven months after failure of internal fixation. Because there is less fibrosis, owing to the fact that there were fewer procedures, the results have been better. There are flexion of 110 degrees and normal extension, but there is no flexion contracture. There are both abduction and adduction as well as rotation. There is a shortening of only 1 inch (2.5 cm.). The patient is able to balance herself on this leg. Her limp is definite, but she has little discomfort—only stiffness and aching after rest. She walks five or six blocks at a time, does her own housework and enjoys fairly good freedom.

Dr. Hugh Smith, Memphis, Tenn.: My series of fifteen monarticular vitallium cup arthroplasties performed on 15 patients is far too small a series from which to draw conclusions. In general I am disappointed with the end results. These have not compared favorably with one hundred and fifty-seven fascial arthroplasties, the majority of which were carried out on solidly ankylosed hips secondary to pyogenic infection or trauma. In this group only 25 per cent failures were expected; consequently, I still lean toward fascial arthroplasty for patients of this type.

On the contrary, cups seem to offer definite improvement in the treatment of malum coxae senile, hypertrophic arthritis, old slipped upper femoral epiphysis and aseptic necrosis of the head of the femur after trauma. While I have not performed any bilateral cup arthroplasties for atrophic arthritis, my experience with thirty-seven bilateral fascial arthroplasties leads me to believe that no method will effect a high percentage of satisfactory results.

The most disappointing feature of cup arthroplasty is the tendency toward excessive periarticular fibrosis. Patients treated by arthroplasty who two months after operation were making satisfactory progress in increase of motion have regressed to an unsatisfactory range at four to six months. Three cups have been removed and the hips manipulated at three, nine and sixteen months, respectively. This procedure has been followed by a material improvement in function. In the future I expect to remove all cups, on the assumption that a permanent metallic joint surface cannot be physiologic, regardless of how well it may be tolerated.

My attitude at present is neither one of indiscriminate condemnation nor one of unqualified enthusiasm. Rather I wish to maintain a state of openminded, liberal indecision until my experience and that of others is more extensive.

Dr. Carl E. Badgley, Ann Arbor, Mich.: I am surprised that Dr. Baker should select primarily cases of arthritis for the use of the vitallium cup. I think, as Dr. Smith-Petersen has said, that the arthritic joint is the worst type of joint on which to employ arthroplasty, regardless of whether the old method or the method of the vitallium mold is used. I am surprised also at the report of Dr. Smith that a traumatic lesion of the hip is better treated by fascial arthroplasty than by the vitallium cup. I have had a series of about 60 to 75 cases in which vitallium cup arthroplasty was done. This treatment of aseptic necrosis of the hip after traumatic dislocation or after fracture of the neck of the femur has given not 25 per cent flexion, which the authors accept as a successful result, but an almost unrecognizable fault in the hip with an excellent range of motion and an excellent gait (except that all have a gluteal gait; this, however, is obviated by the trick movement that all the patients soon learn, that of kicking off with the achilles tendon). Similarly, congenital dislocations of the hip, the old ones with displacement, have done remarkably well with treatment by vitallium cup

arthroplasty. In several cases of fracture dislocation of the acetabulum an excellent range of motion has been obtained, with a gait that would defy almost any one to diagnose as hip difficulty.

The attitude of patients after arthroplasty with the vitallium mold, their comfort the day after operation and their ability to move the hip are so entirely different from those of patients after fascial arthroplasty that there is no comparison. I had 2 cases of spondylitis rhizomelica in which I had successful results in treating the right hips by fascial arthroplasty and equally successful results in treating the left hips by vitallium arthroplasty. The end result with fascial arthroplasty was achieved in one year in both of these cases. The end result with vitallium cup arthroplasty (comfort, motion to 90 degrees and good abduction) was obtained in less than four months. These patients were out walking in three months' time, with considerable relief and considerable motion. The time is greatly lessened by the use of vitallium arthroplasty.

In treating an infectious or a proliferative process, as in cases of atrophic arthritis, there will be trouble whether vitallium cup arthroplasty or fascial arthroplasty is used because there is a regeneration of the capsule. It is of the greatest importance that the cup be long enough to extend to the margin of the vastus muscles so that there will be no exposure of the neck and so that capsular adhesion to the neck cannot occur. In cases of arthritis in which another operation was required after vitallium cup arthroplasty because of increased stiffening of the hip, I have always found that the capsule was glued to the neck. That was the failure of the Venable cup, which, with its flanges, allowed a space through which the capsule could become glued, through these openings to the neck.

The use of the vitallium cup is one of the most efficient steps in arthroplasty of the hip that I have seen.

Dr. Lenox D. Baker, Durham, N. C.: Dr. Smith-Petersen has reemphasized the importance of the patient's cooperation. He has pointed out also the importance of meticulous operation, especially in shaping the head of the femur and the acetabulum. Dr. Waters and I feel that the most careful work should be done on the soft parts as fibrosis has been the main difficulty in our unsatisfactory cases.

We believe, too, that it is necessary to have a freely movable surface on both sides of the cup; this is shown by the fact that we now use the Smith-Petersen cup. However, it has been of interest to us that in both instances in which Venable cups have been removed the articular surfaces were smooth on the head of the femur as well as in the acetabulum.

Dr. Taylor presented another use for the vitallium cup, but according to our classification, the results in his 2 cases would be classed as poor because the patients gave positive reactions to the Trendelenburg test.

Dr. Badgley questioned our selection of cases of arthritis. We said in the paper that we were fully aware of the contraindications and the importance of the proper selection of cases. We had eighteen cases; 10 of these were cases of arthritis. In 6 of these the results were good; in 4 they were poor (in 1 they were poor because of infection). There were 7 cases of pyogenic, gonococcic or traumatic joints. In 3 the results were good; in 4 they were poor (in 2, because of infection). We feel that the vitallium cup procedure has a marked advantage over the fascial arthroplasties in that it offers some hope to the badly crippled patient with arthritis.

LEG-SHORTENING OPERATION FOR EQUALIZING LEG LENGTH

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NEW YORK

Unequal leg length has always been an important and common orthopedic problem. It may be due to any of a variety of causes and in a large proportion of cases can be prevented. Joint dislocation, shortening or overgrowth of one bone or of the whole extremity may be responsible. Congenital dislocation of the hip is the most common cause of unequal leg length in infancy, but congenital shortening or absence of one or more bones may occur. Congenital dislocation can usually be corrected by early reduction. Suppurative arthritis of the hip, especially if drainage is delayed, often results in partial or complete absorption of the femoral head and neck, or partial or complete dislocation of the hip, with resultant shortening. Such shortening can usually be prevented by early adequate drainage of the original focus and of the joint and chemical treatment of the infection. Arthritis or osteomyelitis may sufficiently damage the epiphysial disk to disturb growth, especially if drainage is delayed. A fracture with angulation or overriding may cause shortening of a leg, although the modern treatment of fractures promises to eliminate this cause. War injuries with immediate or surgical removal of masses of bone may result in serious shortening. Congenital coxa vara, coxa plana, and slipping of the upper femoral epiphysis may result in some shortening, although early recognition and prevention have greatly reduced the incidence of shortening due to slipping of the femoral epiphysis. Hemiatrophy and hemihypertrophy account for occasional cases of leg inequality; included in the group due to hemihypertrophy are cases of arteriovenous aneurysm, hemangioma and neurofibromatosis. Surgical treatment of aneurysm and operation or radiotherapy for hemangioma may limit the shortening. Tumors requiring bone resection may result in shortening unless bone grafting can be used. Infantile paralysis is still the most common source of shortening of the leg in this country, and no preventive method has been found, although growth of the longer leg can be limited. Prevention of the disease itself or of the

From the New York Orthopedic Dispensary and Hospital.

Read before the Section on Orthopedic Surgery at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 4, 1941.

accompanying paralysis offers greater promise for the future. Thus shortening is far more common than elongation of the leg and can in many cases be prevented.

EFFECTS OF LEG INEQUALITY

Inequality of leg length of less than an inch (less than 2.5 cm.) causes little or no assymetry of the body or limp and rarely any discomfort. It may be an advantage to patients with certain types of scoliosis, a stiff extended knee, a stiff abducted hip, weak hip abductor muscles, a long leg brace or talipes equinus. A difference of 1 or 2 inches (2.5 or 5 cm.) usually causes a noticeable limp and assymetry of the body, but this difference can be easily corrected by tilting the pelvis or elevating the heel and possibly the sole of the shoe. An inequality of 2 inches (5 cm.) or more prevents the patient from standing with the legs together unless the hip and the knee are flexed on the long side and consequently interferes with the patient's walking, running, dancing and sports. Compensation is possible with a cork-soled shoe or patten and in cases of marked shortening, with a double shoe or extension brace; however, these devices are clumsy, expensive and unsightly. Scoliosis, a deformed and ankylosed hip or knee, or weak leg or trunk muscles may further complicate marked leg inequality, while the faulty mechanics of the short leg may cause pain in an unstable lumbosacral joint, hip or knee. Accordingly, it is desirable to prevent leg inequality so far as it is practical and to correct the inequality when the amount of shortening and the degree of disturbance warrant correction. Associated deformities should usually be corrected before the shortening operation is undertaken; for example, subtrochanteric osteotomy for hip adduction deformity should be performed before leg shortening is attempted.

METHODS OF CORRECTION

There are several methods of minimizing or correcting leg inequalities. The simplest procedure is the stimulation of the growth of the epiphysis of the shorter leg by drilling or the insertion of irritants or the retardation of the growth of the longer leg by roentgen irradiation. Unfortunately, none of these methods has been uniformly or sufficiently successful, and none can be accurately controlled, but the possibilities of such treatment have not been exhausted. The growth of the longer leg may be slowed by obliterating an epiphysial disk by the operation of Phemister or one of its modifications, or growth may be essentially stopped by obliterating all of the epiphyses. This operation is relatively simple and safe and is certainly the method of choice for the growing child, even if only partial correction is obtained. The difficulty of

judging the proper time for the operation and the number of epiphyses to treat has been partly eliminated by use of the formulas obtained from a number of studies of leg growth in children and relation of these formulas to the height of other members of the family. Probably no exact method, infallibly applicable in each case, will be discovered for determining the eventual length of the leg. Should epiphysial exeresis

Fig. 1.—N. H., a girl 14 years of age, had a tuberculous hip. The leg was 4¾ inches (12 cm.) short. Two inches (5 cm.) was resected with 1 inch (2.5 cm.) step cut osteotomy and intramedullary peg fixation. Slight separation of fragments occurred with 15 degrees recurvatum and 15 degrees varus deformity. *A*, immediately after operation; *B*, five months after operation.

fail to equalize the leg length, the short leg may be lengthened directly by osteotomy followed by traction in a special apparatus such as the one first described by Putti and modified by Abbott. Leg lengthening has the advantage of restoring the affected bone or leg to normal length

and the patient to normal height without risking damage to the "good" leg. It is less suitable if the long leg is the abnormal one, if the patient is tall or if the short leg is considerably affected by paralysis, atrophy or deformity. The operation is technically difficult and beset with complications, and the convalescent period is long. It is not my province to discuss it further here.

Finally, unequal leg length may be partly or completely corrected by shortening the longer leg. Legs have been accidentally shortened by fracture with overriding since the beginning of vertebrate life. It has long been known that considerable shortening may occur with only temporary reduction in muscle or joint function. Deliberate controlled shortening by osteotomy with overriding or bone resection is natural and logical.

HISTORY OF LEG-SHORTENING OPERATIONS

In 1847, Rizzoli reported a femoral osteotomy with overriding of the fragments for correcting leg inequality; and Mayer, in 1850, and Sayre, in 1863, each reported a similar case. No other mention of the operation has been found until 1907, when Glaessner [1] reported 2 and Deutschländer [2] 3 cases in which the operation of Heine was used. Deutschländer fixed the fragments with an aluminum plate and two screws. In 1916, Taylor [3] mentioned experiments on cadavers with plates, mortises and intramedullary and transfixion pegs. In 1917, Shands [4] reported a case in which resection was done and wire suture was used. In 1918, Calvé [5] described three methods of fixing the femoral fragments: (1) by mortise and tenon, (2) by impacting the tenon into the medullary cavity of the upper fragment and (3) by a double mortise and tenon. He reported 2 cases in which he had used the third operation. In 1918, Fassett [6] described the use of a Lane plate in 3 cases, and a tongue and groove osteotomy in 1. In 1923, Royle [7] reported 4 resections with which intramedullary pegs were used

1. Glaessner, P.: Die Kontinuitätsresektion der langen Röhrenknochen zur Ausgleichung von Verkurzungen, Ztschr. f. orthop. Chir. **30**:39, 1908.

2. Deutschländer, C.: Die Heinische Operation der Kontinuitätsverkurzung zwecks Ausgleichung von Längendifferenzen der unteren Gliedmassen, Ztschr. f. orthop. Chir. **19**:47, 1908.

3. Taylor, R. T.: Shortening Long Legs and Lengthening Short Legs: A New Surgical Procedure, Am. J. Orthop. Surg. **14**:598, 1916.

4. Shands, A. R.: Shortening the Long Leg, Internat. J. Surg. **30**:273, 1917.

5. Calvé, J., and Galland, M.: A New Procedure for Compensatory Shortening of the Unaffected Femur in Cases of Considerable Assymetry of the Lower Limbs (Fractures of the Femur, Coxalgia, etc.), Am. J. Orthop. Surg. **16**:211, 1918.

6. Fassett, F. L.: An Inquiry into the Practicability of Equalizing Unequal Legs by Operation, Am. J. Orthop. Surg. **16**:277, 1918.

7. Royle, N. D.: The Treatment of Inequality of Length in the Lower Limbs, M. J. Australia **1**:716, 1923.

and 1 with which a Lane plate was employed. In 1926, Ritter [8] mentioned resection with the use of intramedullary pegs.

The first shortening of the tibia and the fibula was described by Brooke [9] in 1927 with a report of 2 cases. He used a tibial inlay graft after resection, and he described a step cut osteotomy of the femur, in which beef bone screws were used for fixation. In 1931, Groves [10] described 2 cases in which the intramedullary tenon method of Calvé was used, and in 1933, Moore [11] added 13 cases in which a similar operation

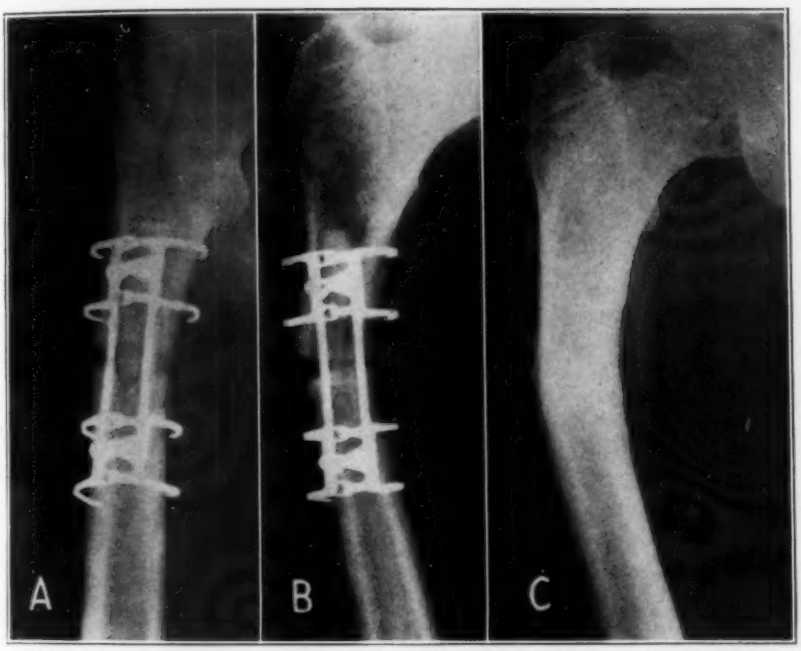

Fig. 2.—H. C., a young man 17 years of age, had a tuberculous hip. The leg was 5 inches (12.7 cm.) short. Two and a half inches (6.4 cm.) was resected, and intramedullary peg and Smith clamp fixation was done. There was 15 degrees varus deformity. Three months after operation the clamp was removed. *A*, immediately after operation; *B*, three months after operation; *C*, three years and ten months after operation.

8. Ritter, R. O.: Technique of Equalizing Leg Length, Surg., Gynec. & Obst. **43**:93, 1926.

9. Brooke, J. A.: Shortening of Bones of the Leg to Correct Inequality of Length, Surg., Gynec. & Obst. **44**:703, 1927.

10. Groves, E. W. H.: An Address on Stature and Poise: The Problem of Unequal Legs, Brit. M. J. **2**:1, 1931.

11. Moore, J. R.: Tibial Lengthening and Femoral Shortening, Pennsylvania M. J. **36**:751, 1933.

was performed. In 1933, Camera [12] reported the first large series, 32 cases in which the condition was treated by resection and the use of a diamond-shaped intramedullary peg. In 1935, White [13] reported 45 cases of osteotomy with overriding. In the first cases he fixed the fragments with wire bands; later he fixed them with two transfixion pins protruding through the wound. In 1936, Brooke [14] reported 4 cases (2 of the tibia and fibula) in which Lane plates were used, making a total in the literature of 10 cases in which plates were used. In 1940, Harmon and Krigsten [15] reported the use of an intramedullary peg with onlay grafts. Thus the leg has been shortened by osteotomy with overriding, resection or step cutting, and the fragments have been fixed by various types of intramedullary or transverse pegs, onlay or inlay grafts, mortise and tenon, or tenon with intramedullary impaction, wire sutures or metal plates.

OPERATION AT THE NEW YORK ORTHOPAEDIC DISPENSARY AND HOSPITAL

The leg-shortening operation was first used at the New York Orthopaedic Dispensary and Hospital in 1928 by Dr. H. L. Von Lackum, who shortened the femur of a 20 year old woman with infantile paralysis 3 inches (7.6 cm.) by a step cut osteotomy with the insertion of an intramedullary bone peg. In the following twelve years (to December 1940), 16 more osteotomies were done for shortening the femurs of 15 patients.[16] In the first case, although the legs were equalized, subsequent reduction and fusion of the subluxated hip on the opposite side were done, which required a 1 inch (2.5 cm.) shortening of that leg. The patients ranged in age from 13 to 23 years, the average age being 18 years. Two of the patients were boys, and fourteen were girls. The cause of the shortening was tuberculosis of the hip in 6 cases, tuberculosis of the knee in 1, infantile paralysis in 5, suppurative arthritis of the hip in 2, congenital dislocation of the hip in 1 and Ollier's disease

12. Camera, U.: 32 casi di accorciamento dell'arto inferiore sano a scopo ortopedico: indicazioni, tecnica, resultati, Chir. d. org. di movimento **17**:569, 1933; Le raccourcissement opératoire du membre inférieur sain dans la grande boiterie due à l'inégalité de longeur des deux membres, Bull. et mém. Soc. d. chirurgiens de Paris **24**:247, 1932.

13. White, J. W.: Femoral Shortening for Equalization of Leg Length, J. Bone & Joint Surg. **17**:597, 1935.

14. Brooke, R.: Bone Shortening for Inequality of Length in the Lower Limbs, Proc. Roy. Soc. Med. **30**:441, 1937.

15. Harmon, P. H., and Krigsten, W. M.: The Surgical Treatment of Unequal Leg Length, Surg., Gynec. & Obst. **71**:482, 1940.

16. Dr. B. P. Farrell worked on the early cases and encouraged the preparation of this study.

in 1. These patients desired the leg shortening because of the limp, the necessity of wearing a raised shoe and the associated assymetric and undesirable appearance of the foot and leg. Pain was of little consequence. Partial disability for walking, running, work and play was a factor in most of the cases. The long leg was usually completely sound except for minor involvement in the patients with infantile paralysis.

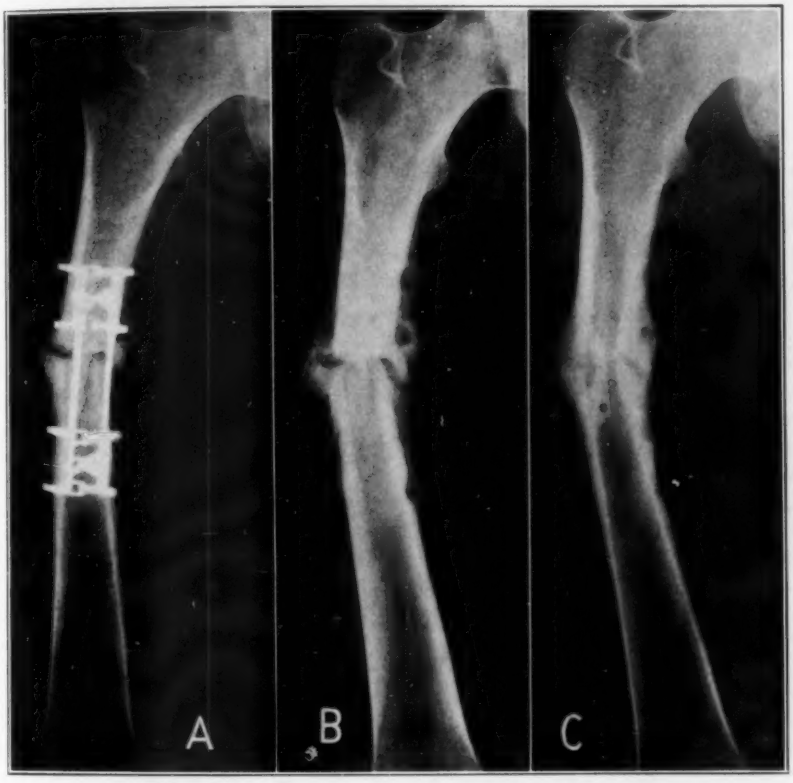

Fig. 3.—S. P., a young woman 18 years of age, had a tuberculous hip. The leg was 4 inches (10.2 cm.) short. Two and three-eighths inches (6 cm.) was resected, and intramedullary peg and Smith clamp fixation was done. The callus was fractured when the cast was removed three and a half months after operation. The clamp was removed. There was 15 degrees varus and recurvatum deformity. *A*, three and a half months after operation; *B*, four and a half months after operation; *C*, eight and a half months after operation.

TECHNIC OF OPERATION

The first 3 operations were osteotomies with resection and end to end (2 cases) or step cut (1 case) apposition; 2 were in the midshaft with an intramedullary peg, and 1 was supracondylar. In the first case 10 degrees valgus and 10 degrees

recurvatum of the fragments occurred in the plaster spica, with partial separation and ¼ inch (0.6 cm.) overriding of the fragments, but union was not delayed. The supracondylar osteotomy resulted in 20 degrees varus and 15 degrees recurvatum of the fragments with ¼ inch (0.6 cm.) overriding due to posterior displacement of the lower fragment, but prompt union occurred. The third osteotomy was followed by 15 degrees recurvatum, with ¼ inch (0.6 cm.) separation of the fragments, and 10 degrees varus, while the osteotomy line persisted for nearly six months. Due to the difficulty in controlling the alinement and the contact of the fragments in the first 3 operations, a Smith clamp, as well as an intramedullary peg, was used for the next 3 femurs (1934). Slight separation of the fragments occurred in 1 case, and 15 degrees angulation in the other two, while solid union required five to eight months. In view of these difficulties, the use of the 5 inch (12.7 cm.) six screw Lane plate was begun in November 1934. The old style plate was used in the first case, with tapered screws through only one cortex; a gap of ⅜ inch (0.96 cm.) and valgus of 10 degrees were present between the fragments, but solid union resulted. The newer type vanadium steel plate was used in each of the following 10 cases, with a step cut Z osteotomy near the midshaft. The femur was shortened 1¾ to 3½ inches (4.5 to 8.9 cm.), (average, 2½ inches [6.4 cm.]). The prongs of the step cut were ½ to 2½ inches (1.3 to 6.4 cm.) long, (average, 1.6 inches [4 cm.]). One plate broke on removal of the spica at four months and was removed, but solid union was present one month later. A second plate, applied with 5 degrees angulation and ¼ inch (0.6 cm.) separation of fragments, broke at five months, allowing closure of the gap followed by prompt union; this plate was removed at seven months, but union was not mature until one year after the shortening. The remaining plates were well applied, and solid union occurred in from three to six months, with unsupported weight bearing at five months. Onlay grafts from the resected bone were used in addition to the plate in 1 case; a large mass of callus resulted, but union was no more rapid than in the other cases.

The technic of the leg-shortening operation is as follows: The midfemur is exposed by an anterolateral incision through the vastus lateralis and vastus intermedius muscles. Osteotomy is done with drill holes and osteotome or with a circular or reciprocating saw. It is important when a motor saw is used to avoid burning the bone or leaving it glassy smooth. The step cut may be made before or after the femur is divided and the fragments fitted accurately together. The plate is shaped to fit the fragments closely without force. The fragments and the plate are held apposed with Lambotte, Heitz-Boyer or Jackson clamps while holes are drilled perpendicularly through the plate holes and both cortices of the femur. The drill is of the exact diameter of the shaft of the screw (exclusive of threads). Self-tapping untapered screws are used, threaded from end to end. They are driven carefully, to avoid stripping the bone threads as the tapping is done, and yet snugly. The screw should be just long enough to penetrate the opposite cortex when the screw is set. It is preferable to have two (or more) of the screws traverse both tongues of the step cut, and the screws should pass at least ¼ inch (0.6 cm.) from the cut ends. The fragments should be firmly held on completion of the plating. These principles of plating have been adopted from the fracture service of Darrach and Murray at the Presbyterian Hospital in New York. It is planned in the future to use the stainless steel plates recommended by them. Their modified Lane technic has not been used because the leg short-

enings are done on nontraumatized tissues, but care and gentleness are considered most important.

A double spica from the midthorax to the toes of the affected side was used in most cases, but a single spica may be used for a thin person, particularly if the hip is fused. The spica is removed for roentgen treatment at the end of three months and is usually left off; the patient is allowed a week or two in bed for the return of muscle power and joint motion; then walking without weight bearing is begun with a walker or crutches. Massage, heat and underwater and other exercises are used for several weeks after the plaster is removed.

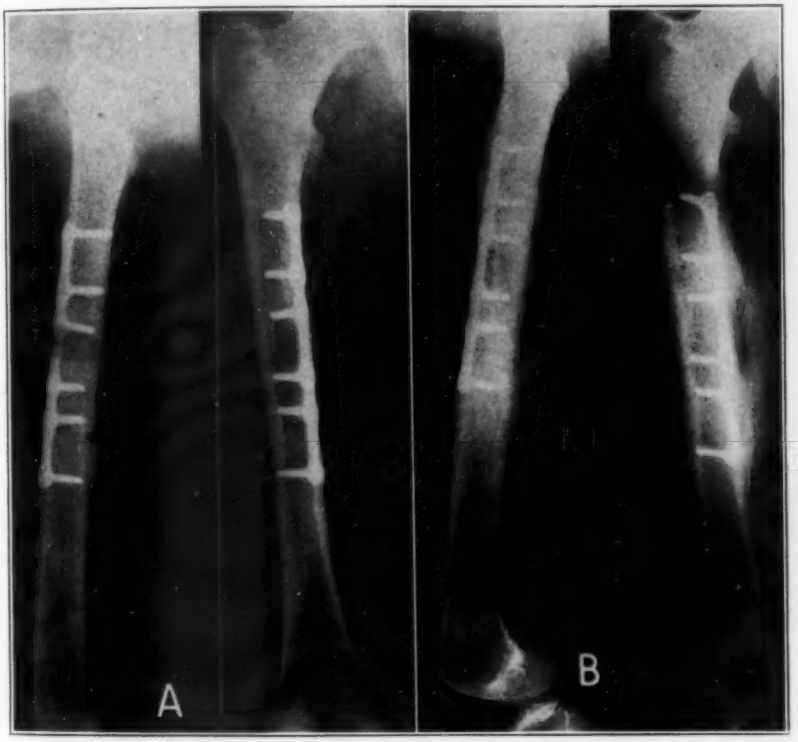

Fig. 4.—E. V., a girl 13 years of age, had tuberculosis of the left knee, which had previously been resected. The leg was 7½ inches (19 cm.) short. The left tibia was lengthened 2⅝ inches (6.7 cm.). One inch (2.5 cm.) resection of the right femur was done, and there was an overlapping of 2½ inches (6.4 cm.). Excellent alinement of the plate and the fragments was obtained, and solid union occurred in three months. *A*, three months after operation; *B*, six months after operation.

RESULTS

These 16 patients (with 17 femoral shortenings) have been followed for one to eleven years (average, four and a half years). There were no infections of wounds, no deaths and no nonunions. The 1 case in which a poorly applied plate held the fragments apart until the plate broke

may be considered an instance of delayed union. Two of the early unplated femurs had an overriding of ¼ inch (0.6 cm.). Angulation of 5 to 15 degrees occurred in 7 cases, but plates were used in only 2 of these. Hip and knee motion and muscle power returned to normal within six months after operation in every case. The residual leg inequality varied from nothing to 2 inches (5 cm.), averaging ½ inch (1.3 cm.). In 1 case, in which there was a total shortening of 7½ inches (19 cm.), the opposite tibia and fibula were lengthened 2½ inches (6.4 cm.), while the femur was shortened 3 inches (7.6 cm.). The limp was greatly reduced or eliminated in all cases but 1; the patient in this case was a girl with extensive poliomyelitis who felt that she had not benefited by the operation. Built-up shoes were discarded in all but 2 cases, and in these the lift was reduced. The appearance of all patients was improved, and none complained of shortened stature. Capacity for walking and more strenuous activities was usually improved; several of the patients were able to participate in all sports. Thus 11 cases of successful leg shortening with step cut osteotomy and Lane plate are added to the 10 cases of simple osteotomy or resection with the use of some type of plate reported in the literature. The same technic, possibly with transverse instead of step cut osteotomy, should be equally applicable to the tibia. However, in most cases all or most of the shortening occurs in the femur, and since it is desirable to have the knees opposite each other for appearance as well as mechanical efficiency, it is preferable to shorten the bone which is relatively longer.

INDICATIONS

The leg-shortening operation usually shortens the height of the patient less than the length of the bone removed. If the patient stands with the legs straight without a lift, the shortening of the body is only half the shortening of the leg, as the pelvic tilt is corrected and the opposite leg remains the same. If the patient must stand on the short leg with the knee and hip of the long leg flexed, the body height is not less after the shortening, as the longer leg is then merely straightened. If the subject wears a raised shoe and changes to a regular shoe after the operation, the height is reduced by the amount of the lift. A short person can partially make up for the shortening by wearing higher heels. Removal of several inches from the leg may cause a noticeable shortening of the legs in relation to the trunk. Since most people sit most of their waking hours and leg shortening does not affect the sitting height, there is little disadvantage to most persons in losing 1 to 3 inches (2.5 to 7.6 cm.) of standing height. The physical advantage of lowering the center of gravity (noted by White), especially when the leg is weak, the improvement in walking and other physical activities, as well as the removal of a built-up shoe, more than offset the loss of height. The

operation is not a simple one and must be done with precision and minimal risk of infection or nonunion, but it is a far simpler and safer procedure than leg lengthening. The step cut osteotomy with bone plating offers an accurate method of shortening the femur and maintaining good alinement. Solid bony union occurs in a reasonable time,

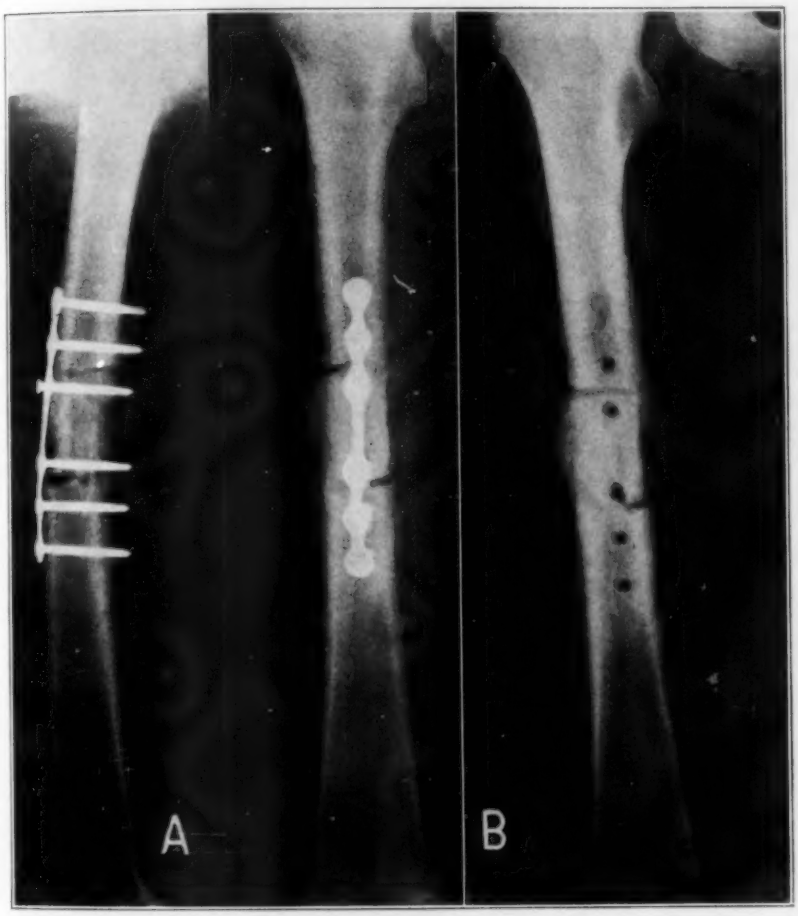

Fig. 5.—M. B., a girl 15 years of age, had a congenitally dislocated hip. The leg was 2½ inches (6.4 cm.) short. One inch (2.5 cm.) resection was done with an overlapping of 1½ inches (3.8 cm.); thus 2½ inches (6.4 cm.) shortening was obtained. A vanadium steel plate was used, but the apposition of the fragments and the plate was imperfect. Fracture of the plate and the callus occurred on removal of the cast three months after operation. The plate broke four months after operation and was removed at five months. Prompt union of the fragments followed. *A*, three months after operation; *B*, five months after operation.

and there is a minimum of interference with muscle and joint action. The operation is rarely applicable to children under 12 years of age, because

of the difficulty in predicting the exact difference in adult leg length and total height, and the greater simplicity of epiphysial exeresis. This technic should be suitable for certain types of war injuries to the bones of the leg. Before the operation is undertaken, all the important factors such

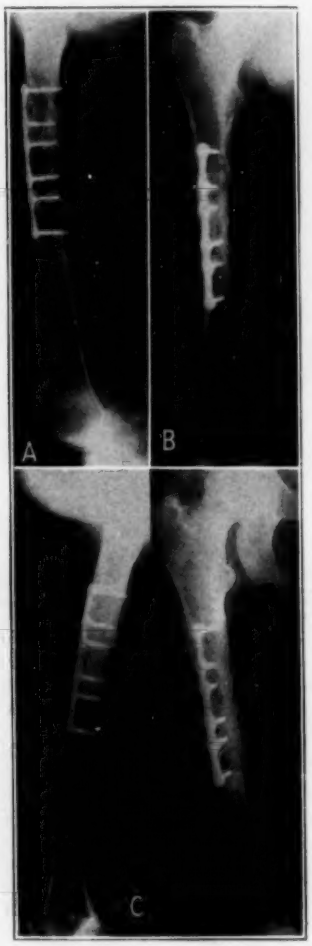

Fig. 6.—R. C., a girl 15 years of age, had infantile paralysis. The leg was 3¼ inches (8.3 cm.) short. There was an overlapping of 3 inches (7.6 cm.). A vanadium steel plate and several small onlay grafts were used. Probably the fastest and most solid union in the entire series occurred in this case. *A* and *B*, immediately after operation; *C*, five months after operation.

as age, sex, occupation total body height, leg length discrepancy, associated deformity, weakness, ankylosis and physical performance should be evaluated.

SUMMARY AND CONCLUSIONS

The causes, prevention and effects of leg inequality are discussed, and the methods of correction are briefly described and evaluated. The history of the leg-shortening operation is given, including the different methods of shortening the bone and of fixing the fragments.

Seventeen leg-shortening operations are reported, including 11 step cut osteotomies with Lane plate fixation. The technic of the operation and the postoperative care are described.

The results of the 17 operations are good. Infection or nonunion has not occurred. The effect of the shortening is discussed.

The step cut osteotomy with Lane plate fixation is recommended as an effective and precise method of shortening the leg and securing prompt and strong union of the fragments.

ABSTRACT OF DISCUSSION

DR. JOSEPH A. FREIBERG, Cincinnati: I think it is generally understood that the indications for leg shortening—leg equalization—are definite but that the number of cases is relatively small. This is evident from the fact that in a clinic such as Dr. Howorth's there were only 17 cases during a period of twelve years.

There are many pros and cons as to the choice of method. It has always appealed to me and to a number of men that one of the better methods of leg shortening entails the simplest operative procedure and leaves in no foreign material. I refer to Dr. J. Warren White's method of stripping the periosteum, overlapping the bones after osteotomy and holding them with simple wire pins which extend through the wound and are later to be removed. This has the advantage that the bones are never held apart and there is always bony contact. In the beginning, until the overlapping bone fragments are partly absorbed and alined in the healing callus, the result will appear rather crude on roentgen examination. Nevertheless, I do not believe any prettier end results can be seen than those shown by Dr. Howorth.

In Cincinnati the Phemister procedure is used to a great extent because the majority of children treated are still growing and by the time they reach the end of their growth period, when this procedure cannot be done, the difference in leg length in any number of cases is small.

TRANSPLEURAL ESOPHAGOGASTROSTOMY

REPORT OF A SUCCESSFUL CASE

A. F. JONAS JR., M.D.
OMAHA

A malignant tumor at or near the junction of the esophagus and the stomach when operable is best treated by transpleural resection and esophagogastrostomy. Such an operation permits wide extirpation of the growth and the regional lymphatics and allows the patient later to swallow and pass food into the stomach in a normal manner. Since Voelcker [1] in 1908 successfully performed esophagogastrostomy after abdominal resection of a carcinoma of the cardiac end of the stomach, the operation has been successfully performed in 21 additional cases. A good summary of the literature on the subject was published in 1938 by Adams and Phemister.[2] In 1941 Garlock [3] gave an account of his clinical experience with the problem. The procedure hereinafter reported follows closely the method described in 1940 by Carter, Stevenson and Abbott.[4]

In the past the operation has more often resulted in failure, with death from shock or infection, than in success. Accordingly, it may be of importance to consider a few technical details. The patient, often greatly debilitated, must be brought into the best possible preoperative condition. In cases of complete obstruction jejunostomy for feeding is indicated. Preliminary pneumothorax allows the wide exposure necessary and provides sufficient room for work within the pleural cavity. The operation must be sufficiently radical to extirpate the regional lymph nodes at the cardioesophageal junction. However, too much of the esophagus cannot be mobilized, or its segmental blood supply will be destroyed and mediastinitis eventuate. The anastomosis must be so made that cicatricial stenosis will not result. The stomach, the upper

From the Department of Surgery, Johns Hopkins University School of Medicine and Johns Hopkins Hospital.

1. Voelcker: Ueber Extirpation der Cardia wegen Carcinoms, Verhandl. d. deutsch. Gesellsch. f. Chir. **37**:126, 1908.

2. Adams, W. E., and Phemister, D. B.: Carcinoma of the Lower Thoracic Esophagus, J. Thoracic Surg. **7**:621, 1938.

3. Garlock, J. H.: The Problem of Carcinoma of the Cardiac End of the Stomach, Surg., Gynec. & Obst. **73**:244, 1941.

4. Carter, B. N.; Stevenson, J., and Abbott, O. A.: Transpleural Esophago-Gastrostomy for Carcinoma of the Esophagus and for Carcinoma of the Cardiac Portion of the Stomach, Surgery **8**:587, 1940.

end of which is left in the thorax, should be anchored securely to a rib so that the suture line will be subjected to no tension. After the thoracic operation, abdominal gastrostomy for feeding should be done if preliminary jejunostomy has not previously been carried out. However, preliminary gastrostomy should never be done, for it seriously limits the mobility of the stomach so that this organ cannot be drawn up into the chest. Food and drink should not be allowed by mouth for at least a week, and during the first postoperative days swallowed saliva should be aspirated from the esophagus by means of a small indwelling tube, for Dragstedt [5] has shown that in dogs with experimental esophageal obstruction the saliva overflows from the full esophagus into the bronchial tree and gives rise to pneumonia. The generous administration of blood, plasma or intravenous fluid to combat shock is of course necessary. Chemotherapy should be employed; at present the drug of choice is sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole).

REPORT OF CASE

D. P., a 43 year white farmer, was admitted April 14, 1941, complaining of difficulty in swallowing of eight months' duration. On taking solid foods he experienced pain beneath the xiphoid process and promptly regurgitated. He was able to swallow liquids, particularly warm ones, with little discomfort but during his illness had lost about 30 pounds (13.6 Kg.). Roentgenograms had been made, and the patient had been told that he had cardiospasm.

Physical examination showed evidence of marked loss of weight but scarcely any dehydration. A small supraclavicular node was palpated on the left side. The temperature, the pulse rate and the respiratory rate were normal. Examination of the urine yielded negative results. The Wassermann test was negative. The blood pressure was 114 systolic and 84 diastolic. The hemoglobin content was 98 per cent. The white blood cell count was 8,800. A roentgenogram made after a barium sulfate meal showed a filling defect involving the lower 2 inches (5 cm.) of the esophagus and a large portion of the cardiac end of the stomach. Esophagoscopic examination demonstrated the same obstruction at the lower end of the esophagus, but no biopsy could be made.

Under local anesthesia the supraclavicular node was removed for biopsy, and was reported normal. On April 17, the abdomen was explored with the patient under anesthesia induced with avertin with amylene hydrate, nitrous oxide and ether. Through an upper midline incision a hard round tumor the size of an English walnut was felt at the junction of esophagus and stomach. No regional lymph nodes were palpable, and the liver was free from metastases, but the tumor lay so high that no part of the esophagus was available for intra-abdominal anastomosis. Accordingly, the wound was closed without further intervention.

On April 24, 1,000 cc. of air was introduced into the left pleural cavity; on April 26, another 1,000 cc. Subsequent roentgenograms showed almost complete pneumothorax on the left but no mediastinal shift. On April 28, with the patient under anesthesia induced with avertin with amylene hydrate and ether, operation was carried out; intratracheal positive pressure was used. A left thoracotomy through

5. Dragstedt, C. A., and Mullinix, R. B.: Experimental Esophageal Obstruction, Arch. Surg. **24**:152 (Jan.) 1932.

the seventh intercostal space was extended from the midscapular to the midaxillary line, and the left lung was observed to be about 60 per cent collapsed. After the inferior pulmonary ligament was divided and the phrenic nerve was crushed, the diaphragmatic fibers were split from the esophagus to the lateral chest wall. This afforded a good view of the tumor. A few small nodes were palpable in the nearby fat. The stomach was next drawn through the rent in the diaphragm, and the left gastric and left gastroepiploic vessels were ligated. After the field had been carefully packed off with moist gauze pads, the stomach was divided

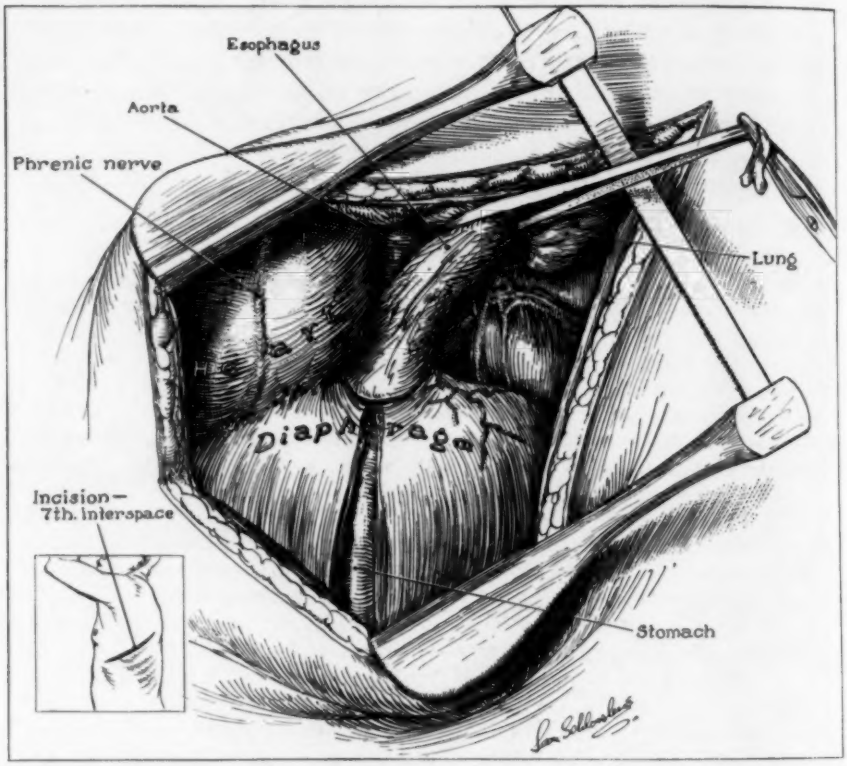

Fig. 1.—Through a posterolateral approach in the seventh interspace, the esophagus is grasped and the diaphragm split.

transversely between two Payr clamps placed an inch (2.5 cm.) below the lesion. The stomach was then closed with a continuous transfixion suture of chromic catgut reenforced by a number of inversion silk sutures. The lower part of the esophagus was similarly divided and ligated with plain catgut, and the tumor was removed. Two transverse incisions were made on the anterior wall of the stomach; the upper was an inch (2.5 cm.) below the line of closure, and the lower was an inch farther down. Through the upper one, the tied end of the esophagus was thrust, and through the lower, its ligature was brought out in order to keep the esophageal opening well within the stomach during the suturing, which was carried out with

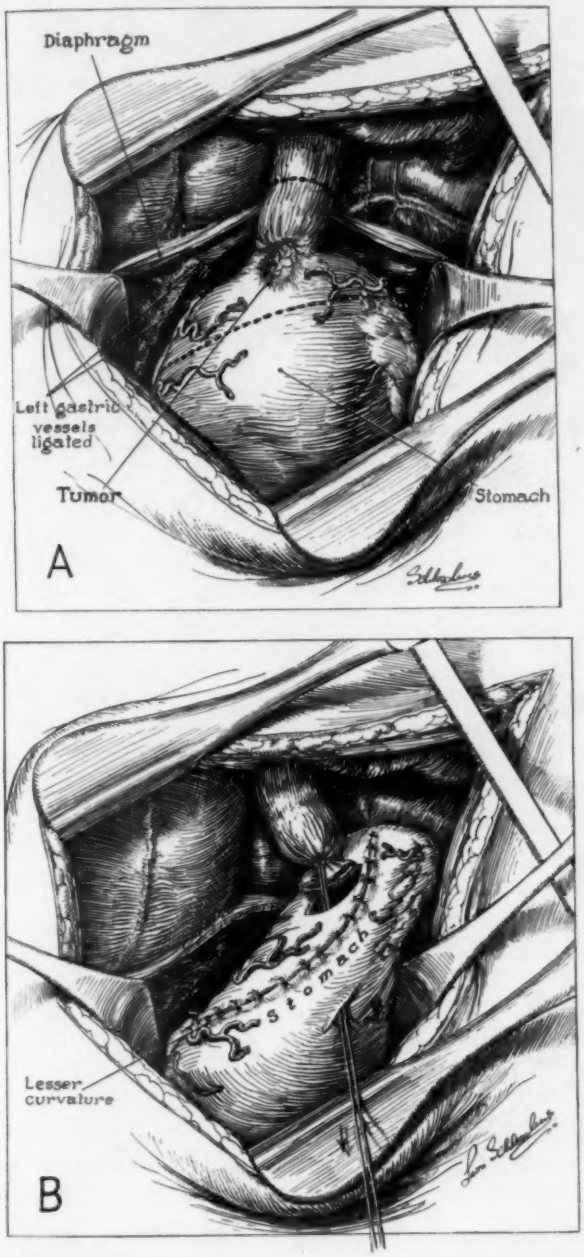

Fig. 2.—*A*, the tumor is exposed and the stomach drawn into the chest; the lines indicate the site of reaction. *B*, the tumor has been resected together with the adjacent portions of the stomach and the esophagus; the stomach is closed with interrupted silk sutures, and the esophagus is implanted into the stomach.

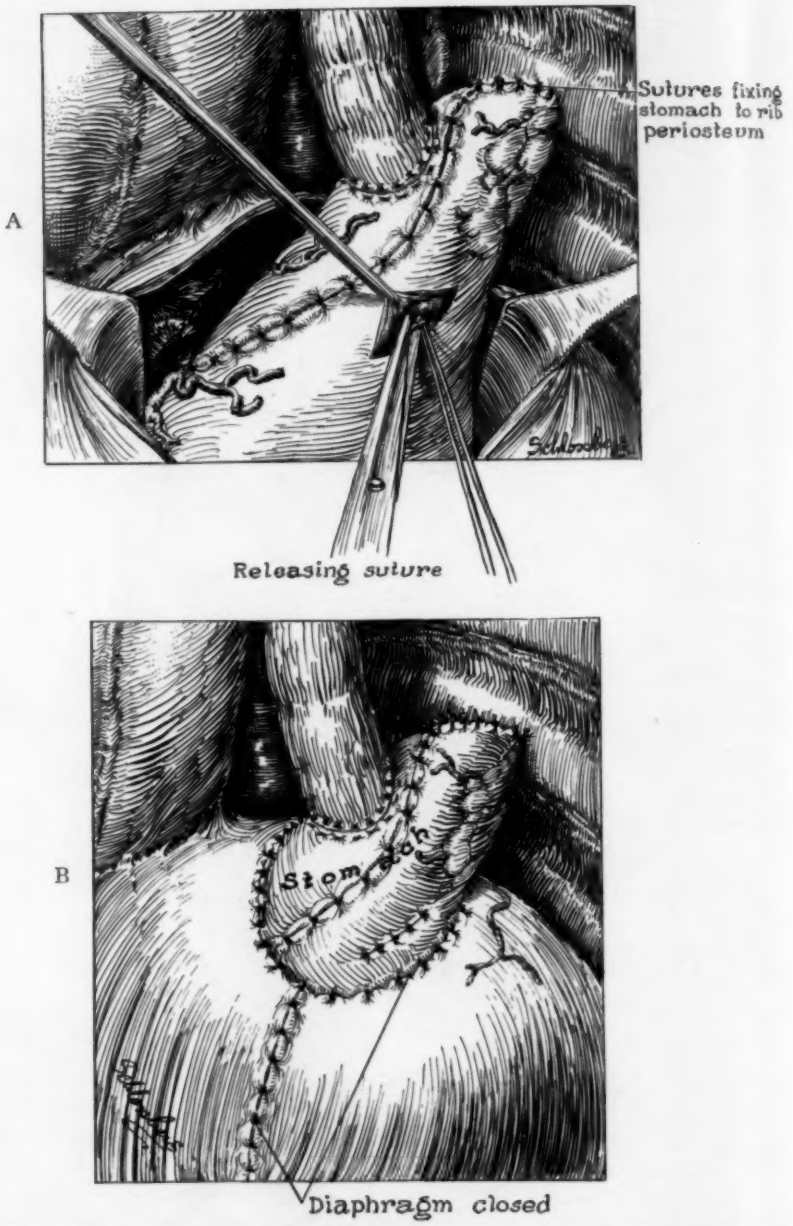

Fig. 3.—*A*, anastomosis with interrupted mattress sutures has been completed, and the lower end of the esophagus has been opened. *B*, the operation is completed; note the sutures fixing the stomach to the rib in order to avoid tension.

two layers of mattress sutures of medium silk. When this had been completed, the catgut ligature was cut in order to allow the esophagus to discharge freely into the stomach. The lower gastric wound was closed with interrupted silk sutures. The diaphragm was sutured snugly about the midportion of the stomach, leaving a conic segment of the stomach within the thorax. This portion of the stomach was then anchored to the costal periosteum in order to relieve the suture line of any tension.

A mushroom catheter was placed in the costophrenic angle at the ninth interspace, and after 8 Gm. of powdered sulfanilamide had been dusted into the field, the chest wall was closed in layers with silk. A small Kader-Senn gastrostomy was finally done. During the operation the patient received 1,000 cc. of citrated blood, 1,500 cc. of 5 per cent dilution dextrose in physiologic solution of sodium chloride and 250 cc. of human plasma. At the end of the procedure he was in good condition.

Sodium sulfathiazole was given intravenously for four days after operation, and a blood concentration of 4 to 9 mg. per hundred cubic centimeters was maintained. Feedings by gastrostomy tube were commenced on the fourth day, and thereafter sulfathiazole also was given by this route. Adequate fluid intake was maintained by the intravenous route. On the third night after operation the temperature rose to 101 F., but thereafter the patient was afebrile. The esophageal tube was removed on the seventh day, and fluid by mouth was first allowed on the eleventh day. On the fourteenth day thoracentesis yielded 550 cc. of blood-tinged fluid, which was sterile on culture. On the twenty-sixth day a roentgenogram made after a barium sulfate meal showed a wide well functioning stoma between the esophagus and the stomach. The wound healed by first intention and the patient was discharged on May 31 with the gastrostomy tube still in place. The pathologic diagnosis was adenocarcinoma extending into the esophagus and to two of the regional lymph nodes.

The patient returned one month later with definite empyema low on the left side of the chest. A short segment of the ninth rib was resected; the empyemic cavity was drained (Bacillus coli), and the patient was discharged after removal of the gastrostomy tube. When last heard from, four months after operation, he was eating all kinds of food, had gained 12 pounds (5.4 Kg.) and was doing light work.

COMMENT

The management in the case reported proved essentially satisfactory, and there seems little reason to alter it in the future. After open anastomosis with obvious contamination of the pleural cavity, the occurrence of small empyema is not surprising, although the use of sulfathiazole might provide better protection in another case. Postoperative strictures reported by other surgeons have manifested themselves within the first few weeks, whereas in the present case there was no evidence of stricture after four months and it thus seems unlikely that stricture will develop. During the first few months after operation, the gastrostomy must be kept open (although not used for feeding) in order to provide for retrograde dilation should this become necessary.

REVIEW OF UROLOGIC SURGERY

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(Concluded from page 397)

URETER

Tumor.—Olovson [24] reports benign ureteral tumor in a woman aged 43 years who had pain for two years in the left side of the abdomen. This pain extended into the left renal region. On cystoscopy, a papillomatous growth was seen moving rhythmically in and out of the left ureteral orifice. A ureterogram revealed stenosis of the lower part of the ureter with a filling defect above. The ureteral growth, a benign papilloma, was removed transvesically.

Olovson states that 42 cases of benign ureteral tumor, mostly papilloma, have been reported. The growth is often located in the lower third of the ureter. The chief symptoms are hematuria, pain and a palpable kidney. Hematuria occurs in about 70 per cent of the cases. The filling defect in the ureterogram is a characteristic feature of ureteral tumor, but there is no typical picture suggesting the benign tumor. In the cases of benign ureteral tumor reported in the literature, two operative methods have been found expedient, namely, (1) local

24. Olovson, T.: Gutartige Harnleitergeschwülste, Acta chir. Scandinav. **84**: 469-478, 1941.

treatment by cauterization and ureteral resection and (2) complete nephroureterectomy. The latter method has been employed in the majority of cases. In Olovson's opinion, the local procedure is the ideal method of treatment for benign ureteral tumor.

Stang and Hertzog [25] report 4 cases of primary carcinoma of the ureter. The average age of the patients was 58.2 years. The chief complaints were hematuria and pain in the lower portion of the abdomen. A tumor protruding from the ureteral orifice was noted in 3 of the cases. Ureterograms revealed dilated ureters at the site of the tumor and above the growth. Three of the patients died of metastasis after operation. The fourth is living and well at the age of 75 years, four and a half years after removal of the tumor.

Lazarus [26] states that metastatic tumor of the ureter is extremely rare. Only 18 cases are recorded in the literature, including 1 which he presents. In these cases, 7 tumors originated in the prostate gland, 2 in the bladder, 2 in the cervix, 1 in the urethra, 1 in the stomach, 1 in the bronchus and 2 in the breast. In 1 case, the primary focus was Hodgkin's disease. In Lazarus' case, the primary source was the ovary, which, on microscopic examination, presented malignant changes in a dermoid cyst. The right ureter only was involved in 7 cases, only the left in 5 and both ureters in 6. Metastatic tumor of the ureter must be differentiated sharply from primary tumor and from tumor invading the ureteral wall by direct extension. Such differentiation can only be made histologically by finding tumor cells in the perivascular lymph spaces or within the vessels of the ureter.

Randall [27] reports endometrioma of the ureter in the case of a woman aged 37 years. The patient's illness began a year before the initial examination with a sense of discomfort in the right loin. Immediately prior to examination she had a severe attack of pain in the loin associated with hematuria. Cyclic bleeding was not observed. Menses usually had been regular at thirty day intervals, but in the past year the menstrual intervals had lessened. She always had some pain during and shortly after each period. Urinalysis gave negative results except for a few leukocytes and cells in the blood. Urographic studies revealed a normal left upper renal tract; on the right side, some haziness was present in the shadow of the renal pelvis. In the upper half of the right ureter there were multiple defects, and in the lower half there

25. Stang, H. M., and Hertzog, A. J.: Primary Carcinoma of the Ureter: A Report of Four Cases, J. Urol. **45**:519-526 (April) 1941.

26. Lazarus, J. A.: Metastatic Ureteral Obstruction Following Carcinoma of the Ovary: Report of an Unusual Case of Pyonephrosis Resulting from a Metastatic Carcinoma of the Ureter, J. Urol. **45**:527-535 (April) 1941.

27. Randall, A.: Endometrioma of the Ureter, J. Urol. **46**:419-422 (Sept.) 1941.

was a definite rounded filling defect around which the contrast medium flowed. At cystoscopy, a catheter was passed to the right renal pelvis, and a pyelogram was made; this resulted in the diagnosis of a growth at the lower end of the right ureter. The ureter was exposed surgically, and a fusiform swelling was found in the lower end. The ureter then was freed from the bladder and the kidney and ureter removed through a second incision. The microscopic diagnosis was endometrioma.

Stone.—Spence [28] reviews 24 cases of stone at the ureteropelvic junction. In 23 of the 24 cases, urography revealed functional or anatomic damage to the kidney resulting from stone. Except for diagnostic purposes, the use of cystoscopic procedures is ill advised in cases of this type. This is strikingly brought out in the synopsis of 3 cases in which death occurred. Early surgical removal of stone at the ureteropelvic junction is the treatment of choice.

Osterbye [29] reports 113 cases of ureteral calculus. Ureteral stone occurred most frequently in men between the ages of 20 and 25 years and was usually unilateral. In 90 per cent of the cases, the urine was sterile; gross hematuria occurred in 30 per cent, and hematuria was evident microscopically in 95 per cent. In about half the cases, stone was locked just above the bladder. In 70 per cent of cases, stone will be passed naturally. Osterbye expresses the belief that instrumental treatment should be resorted to without giving expedient treatment a chance. Ureterolithotomy was performed in only 8 of the 113 cases.

Moring [30] reports 140 cases of ureteral stone. He considers chiefly ureteral manipulation and removal of stone. These methods were used in 98 cases (70 per cent); in 41 of these there were almost immediate results. The stone passed naturally in 21 per cent of the cases. Most of the patients had symptoms for only a short time. In 12 cases (9 per cent) some type of surgical procedure was carried out; 6 of the patients were operated on primarily, and the other 6 after cystoscopic methods had failed to bring down the stone.

Moring advises the transurethral method, as there is little risk and less loss of time. Forty-two patients were sent home with the expectation that the stone would be passed. They were followed for six months to five years, and in practically all cases the stone was passed. In most cases the patient did not know that the stone was being passed. Hydronephrosis developed in only a small number of the cases.

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28. Spence, H. M.: Stones at the Ureteropelvic Junction, J. Urol. **45**:579-586 (April) 1941.

29. Osterbye, K.: Disease of Ureters and Its Treatment, Ugesk. f. læger **102**: 1189-1194 (Nov. 14) 1940.

30. Moring, S.: Treatment of Ureteral Calculi, Ugesk. f. læger **102**:1194-1197 (Nov. 14) 1940.

Ureterostomy.—Folsom and O'Brien [31] report 12 cases of cutaneous ureterostomy. This is a simple operation and is well tolerated, even by patients already debilitated from advanced carcinoma. Cutaneous ureterostomy gives satisfactory renal drainage. At present, this seems to be the most practical way of diverting the urine when the ureters are badly damaged by dilatation from obstruction. The authors were impressed by the lack of difficulty experienced by the patients in keeping dry and comfortable.

Ureterocele.—Campbell [32] states that ureterocele is a congenital obstructive lesion in which secondary urinary infection is the important complication. Resulting persistent pyuria, too commonly designated chronic pyelitis, is the symptom which almost always prompts the urologic diagnostic investigation.

Ureterocele is not unusual. It is notable that failure to identify ureterocele in young patients sometimes accounts for premature death. For this reason, the true incidence of the condition is doubtlessly less among adults than among the young.

The clinical picture is almost always that of chronic pyelitis; urinary back pressure pain may be a prominent symptom.

The diagnosis is readily made by urologic examination. Urography is frequently helpful, especially when ureterocele produces a cystographic filling defect.

Removal of the obstruction is the immediate treatment. Eradication of urinary infection, calculi or other complicating lesions is the essential accessory treatment.

BLADDER

Carcinoma.—Paterson [33] discusses roentgen therapy of cancer of the bladder. He states that tumor of the bladder, like tumor in the cervix, the mouth and the skin, can be successfully treated with roentgen rays. He also remarks that this method of treatment is not being used extensively at present, because the limited material does not permit the working out of satisfactory methods of treatment.

Paterson classifies tumor of the bladder from a roentgenologic and therapeutic point of view into three groups: (1) benign papilloma, (2) noninfiltrating cancer and (3) infiltrating cancer. In his cases, this diagnosis was based on contrast cystography and relief pneumocystography.

It is Paterson's opinion that satisfactory roentgen therapy is preferred to surgical operation in all cases, even as a first treatment. He

31. Folsom, A. I., and O'Brien, H. A.: Cutaneous Ureterostomy: A Report of Twelve Cases, J. Urol. **45**:587-597 (April) 1941.

32. Campbell, M. F.: Ureterocele, J. Urol. **45**:598-611 (April) 1941.

33. Paterson, R.: Cancer of the Bladder, Brit. J. Radiol. **14**:219-234 (July) 1941.

describes implantations of radium and condemns the cystoscopic implantation of radon seeds. He discusses the value of roentgen ray single exposure treatment by contact treatment, such as that recently described by Crane and others. This method to be successful requires the use of high doses, small fields and special methods of beam direction.

Cope [34] states that papilloma of the bladder may remain latent for long periods. Painless hematuria, although a common symptom, is by no means the only symptom for which patients seek advice. Retention of urine, frequency of urination, pain on urination or the passage of a piece of growth may cause the patient to consult the physician. Papilloma of the bladder has a great tendency to become malignant. Every patient who has been treated for papilloma of the bladder should be told of this danger in order to insure that he will report regularly for inspection of the bladder. Patients who have carcinoma of the bladder and to whom life has become unbearable from pain and frequency of urination should be given the chance of relief by transplanting the ureters into the rectum.

Hyams and Silberblatt [35] state that hemangioma occurs with relative frequency, not only on the skin or in different regions of the body, such as the liver, the gastrointestinal tract and the muscles, but also in the urinary bladder. It is considered the rarest of all tumors of the bladder.

The authors report a case of hemangioma associated with papillary carcinoma of the urinary bladder. The patient was a man aged 62 years. On cystoscopy, a subsessile growth with coarse villi about 2.5 cm. in diameter was found on the right superior wall of the bladder. In the posterior base, a second and entirely different microscopic growth was seen; this was sessile, bluish and slightly elevated. Later, the bladder was opened, and both tumors were removed. One was definite papillary carcinoma and the other hemangioma.

Priestley [36] states that treatment of carcinoma of the bladder is a controversial subject and undoubtedly will be disputed for some time. Important factors which must be considered in selecting the proper form of treatment in each case of carcinoma of the bladder include the type, the grade, the extent and the site of the lesion, whether it is multiple or single, whether one or both ureterovesical orifices are

34. Cope, V. Z.: Concerning Papillomata of the Bladder, Brit. J. Urol. **13**: 74-82 (June) 1941.

35. Hyams, J. A., and Silberblatt, J. M.: A Case of Hemangioma Coincident with Papillary Carcinoma in the Urinary Bladder, J. Urol. **46**:271-277 (Aug.) 1941.

36. Priestley, J. T.: General Considerations in the Surgical Treatment of Carcinoma of the Bladder with Particular Reference to Total Cystectomy, New York State J. Med. **40**:1441-1445 (Oct. 1) 1940.

involved, the status of renal function, the presence or the absence of serious renal infection and the age and the general condition of the patient. When these various factors are considered, it must first be decided whether approach to the tumor should be transurethral or suprapubic. When this is decided, fulguration, electroexcision, implantation of radium, segmental resection or total cystectomy must be chosen.

In Priestley's opinion, roentgen therapy alone never constitutes the treatment of choice if a more direct attack can be made on the lesion. Until end results have been evaluated more accurately in relation to the various forms of treatment and the physical characteristics of the lesion itself, there will be no accurate information on which to base the proper choice of treatment.

It seems that total cystectomy might be employed to advantage more frequently, although the indications for total cystectomy cannot be stated dogmatically. In Priestley's opinion there are four main types of cases in which this operation might be considered—cases of (1) extensive low grade lesions, (2) low grade lesions of multicentric origin, (3) repeatedly recurring low grade lesions and (4) high grade lesions which, to the best of the physician's knowledge, have remained confined to the bladder. When total cystectomy is employed in these cases, the ultimate results should prove to be more satisfactory than they have been in the past.

Clancy [37] reports a neoplasm complicating diverticulum of the bladder in a man aged 83 years who had had complete retention of urine on several occasions. A cystogram revealed a large diverticulum on the right side of the bladder. The bladder was explored, and the fibrous ring connecting the bladder with the diverticulum was dilated. The patient died thirty days later. At necropsy it was found that the diverticulum contained papillary carcinoma.

Various authors have stated that neoplasms in diverticula of the bladder occur most frequently between the ages of 48 and 76 years. All authors seem to agree that hematuria is the outstanding symptom. The duration of symptoms varied from ten days to three years. The cystoscope and the cystogram are essential aids in making diagnosis. In cases in which carcinoma protrudes into the orifice of the diverticulum, the diagnosis is simplified. When it is possible to introduce the cystoscope into the diverticulum, much uncertainty is eliminated.

Collings and Welebir [38] report a case of osteoma of the bladder in a woman aged 67 years. Six years earlier, she had been treated with radium for carcinoma of the cervix vesicae. Roentgenograms of the

37. Clancy, F. J.: Neoplasm Complicating Diverticulum of the Bladder, J. Urol. **46**:486-490 (Sept.) 1941.

38. Collings, C. W., and Welebir, F.: Osteoma of the Bladder, J. Urol. **46**: 494-498 (Sept.) 1941.

bladder revealed several large round calcified bodies in the region of the bladder suggestive of calcified fibroids. Cystoscopy revealed a tumor mass 3 cm. in diameter in the region of the left ureteral orifice. Several smaller similar masses were found on the floor of the bladder. Through a suprapubic incision, a number of masses were removed from the mucosa of the bladder. These masses were bony; the largest was embedded in the mucosa. Microscopic examination revealed that the tumors were granulomatous. Sections through the tissue disclosed an acellular structure with the outlines of dense bony material. The diagnosis was probable osteoma of the bladder.

McDonald, Doss and Thompson [39] report their study of a group of neoplasms in which, histologically, some portions were suggestive of sarcoma and others were suggestive of carcinoma. It was possible to demonstrate the epithelial origin of the tumor in each of the 9 cases and to disclose that the carcinoma cells assumed characteristics which, if examined histologically, are diagnostic of sarcoma. The short clinical history and the poor results following treatment in these cases attest to the extremely malignant nature of all lesions of this type in the urinary bladder.

Kahle, Vickery and Maltry [40] discuss 2 cases of endometriosis of the bladder. In the first case, the mucosa was not involved, hematuria was not present, and endometrial infiltration was discovered in the course of a gynecologic operation. For this reason attention was not directed to the vesical involvement before operation, and cystoscopy was not carried out. This case is one of the few on record in which pelvic operation did not precede development of the endometriosis of the bladder.

In the second case, in which there had been a previous gynecologic operation, the vesical mucosa was involved, and hematuria had been present at intervals for six years. This case is unusual in that vesicosigmoid fistula developed, although it is not possible to say whether it followed the apparently superficial injury of the sigmoid at the first operation or was the result of the endometrial process.

Cystectomy.—Vest and Curd [41] report the case of a patient with infiltrating epidermoid carcinoma of the bladder which involved the vaginal vault and the uterine cervix. Total cystectomy with panhysterectomy was performed.

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39. McDonald, J. R.; Doss, A. K., and Thompson, G. J.: Carcinoma of the Urinary Bladder Imitating Sarcoma, J. Urol. **46**:38-51 (July) 1941.

40. Kahle, P. J.; Vickery, G. W., and Maltry, E.: Endometriosis of the Urinary Bladder: Report of Two Additional Cases, J. Urol. **46**:52-56 (July) 1941.

41. Vest, S. A., and Curd, H. H.: Total Cystectomy Combined with Panhysterectomy, Surg., Gynec. & Obst. **73**:517-519 (Oct.) 1941.

Urograms revealed that the right kidney was functionless owing to obstruction and hydronephrosis on the left. Preliminary left nephrostomy was followed by relief of symptoms of the bladder and improvement in the patient's general condition. When laparotomy was carried out, evidences of metastasis or involvement of the lymph nodes were absent, but induration of the tumor extended into the region of the cervix and the vaginal vaults.

It was therefore decided to perform panhysterectomy in addition to total cystectomy. This operation was facilitated by ligation of the anterior branch of the internal iliac arteries on both sides. Vest emphasizes the importance of this step in a combined operation of this type.

The patient has learned to care for the nephrostomy tube and fifteen months after operation has shown no evidences of recurrence.

Hyperplastic Lesions.—Stirling and Ash[42] report 22 cases of hyperplastic lesions of the urinary tract. Hematuria, dysuria or frequency of urination was found in every instance and was usually severe. The genesis of glands and cysts and their relation to carcinoma are discussed. Three patients had concomitant cysts and carcinoma of the bladder.

Brunn's follicle is an invagination or an extension of surface epithelium, and its subsequent fate depends on whether epithelial metaplasia progresses to a squamous or a glandular type. Follicular cystitis is a nonspecific entity, common in any chronic infection. Several hyperplastic forms of cystitis may be found in the bladder at the same time.

Stirling and Ash describe for the first time a lesion termed "papillary hyperplasia." It may combine one or more features of the other types, and it is important, since it may simulate tumor.

Lesions of the Nerves.—Hinman,[43] in considering care of the bladder at the front when paralyzed by injuries to the spinal cord, states that the patient is wholly at the mercy of those about him. The initial effect of an injury of the spinal cord, if any, on micturition is the same, no matter at what level of the cord injury occurs. Spinal shock causes muscular atony. The period of urinary disability, however, which is manifested by retention and overflow incontinence, may last only a few days or may persist for many months, depending on the location and the severity of the injury. Recovery from this initial effect likewise is variable with the site and the extent of the lesion. The two effects of injury to the spinal cord are (1) the initial effect of retention and

42. Stirling, W. C., and Ash, J. E.: A Clinicopathologic Discussion of Hyperplastic Lesions of the Urinary Tract, South. M. J. **34**:358-364 (April) 1941.

43. Hinman, F.: The Care of the Bladder at the Front When Paralyzed by Injuries to the Spinal Cord, J. Urol. **46**:499-504 (Sept.) 1941.

overflow incontinence and (2) the variability in the time and the type of recovery; these necessitate two periods of management for these patients. Only one period of management is required for patients with temporary acute retention, while two are necessary for those with a bladder affected by a permanent neurogenic condition. In the first period, management is concerned with initial retention and overflow incontinence common to both groups and the second with the changing types of dysfunction occurring in a certain order, according to which one of the three levels of innervation have been injured and the extent of this injury. The management of retention in the two groups of cases is different.

The method of noninterference, which allows distention and overflow, is a form of neglect occasionally justified by circumstances. It should be attempted only as a temporary expedient when opportunity and facilities for proper care are wanting. It may be the least injurious form of treatment under these circumstances and for the short period which will be required for the patient to reach the place where proper methods can be used. It is an emergency measure and never to be used for long periods. Rarely does an uninfected bladder thus neglected rupture and rarely are distention and overflow incontinence painful to the paralyzed patient. When urinary infection is present, prolongation of distention is extremely dangerous.

The method of manual expression of urine is best for the early attainment of an automatic bladder and, when it works, may save many months of treatment with catheters. It is likewise a method which avoids urinary infection better than any other.

The use of a retention catheter with continuous tidal irrigation has what may seem to be slight advantages over the use of a simple retention catheter or intermittent catheterization. Experience has proved, however, that the prevention of overdistention of the bladder by continuous drainage and reduction of infection by automatic irrigation are advantages not to be had by other methods. Further, the use of a retention catheter with tidal irrigation hastens development of an automatic bladder.

The method of suprapubic cystostomy and continuous tube drainage for the acute initial retention caused by injury to the spinal cord is difficult to appraise. It would seem radical to advise its routine use at the onset of acute retention, but often it is indicated later when manual expression fails, when a urethral catheter will not be tolerated, when virulent urethritis, acute prostatitis, epididymitis or ascending infection develops or when vesical hemorrhage is so severe that it cannot be controlled by the urethral catheter. Hinman states that a safe rule to follow is to insert a suprapubic tube immediately if the injury is severe, no matter what its location, provided it will be days

or weeks before the patient reaches the place where faithful and technical management can be given him. A cystostomy catheter is less injurious than neglect of the many technical procedures required in the successful use of any of the other methods. The entire program of management of the period of acute retention is to prevent ascending urinary infection. Urinary drainage is one method of prevention, and aseptic urinary drainage is the best. Regular periodic manual expression, the use of a retention catheter and suprapubic cystostomy are the only methods for securing continuous drainage with the least risk of pyelonephritis. In civil practice, the method of noncatheterization and manual expression is preferred. If this fails or if infection appears, use of a retention catheter with continuous tidal irrigation is indicated. When this method becomes contraindicated for any of the many reasons mentioned earlier, suprapubic cystotomy is performed. In military practice, however, this order of preference must be reversed, for the sole reason that technical performance of the first two methods is unattainable at the front or evacuation centers. The delay of even a few days to reach a hospital will be too late. A simple suprapubic kit should be part of the surgeon's emergency outfit, and suprapubic cystotomy should be performed at the earliest opportunity for acute retention caused by injury to the spinal cord.

Rudy and Muellner [44] state that neurologic disturbance of the urinary bladder is common in cases of diabetes mellitus. It should be looked for during exacerbation of diabetes among patients with diabetes who have urinary symptoms, who are receiving deficient diets and who have lost much weight. Disturbances of the bladder are frequently associated with other abnormal neurologic signs and symptoms. For properly treated patients, the prognosis is fair.

Treatment should consist of control of the diabetes and administration of a diet which is as nearly normal as possible and is high in vitamins and minerals. Vitamin concentrates, especially vitamin B_1 (thiamine) and those of the B complex, should be used extensively and for prolonged periods. Bladder instrumentation should be avoided in cases in which infection is absent. Constant drainage of the bladder, chemotherapy and urinary antiseptics are of value when infection of the urinary tract is present.

Robinson [45] states that the correct handling of the bladder in cases of injury to the spinal cord is of paramount importance at present. It is obvious that treatment can be based only on a sound appreciation of

44. Rudy, A., and Muellner, S. R.: The Neurogenic Bladder in Diabetes Mellitus: Early Recognition and Treatment with a Report of Cases, J. Urol. **45**: 844-857 (June) 1941.

45. Robinson, R. H. O. B.: The Treatment of the Bladder Following Injury to the Spinal Cord, Brit. J. Urol. **12**:244-248 (Dec.) 1940.

the normal physiology of micturition, so far as this is known, and of the changes that result in the function of the bladder after damage to the cord. After damage to the cord the condition of spinal shock occurs and interferes with the activity of the segmental reflex below the level of the lesion. The effect is greatest in the segments nearest the site of injury and least in those most remote. The duration is variable, and relapse is possible. During the presence of spinal shock, activity of the bladder is interfered with from suppression of the reflex arc; the effect is greatest if the site of injury to the cord is low. Destructive lesions of the sacral segments or of the cauda equina denervate the bladder and reduce it to the autonomous state; as a result, it undergoes hypertrophy; its capacity diminishes, and voluntary control is lost permanently. Anatomic division above the sacral segments cuts off all cortical inhibition, so that emptying cannot be controlled and will take place as soon as the wall of the bladder is stretched sufficiently. Such a bladder is spoken of as the uninhibited reflex type and is the best end result that can be expected after complete section of the cord. Intercurrent infection may cause spinal shock to recur at any time and may result in the bladder regressing to a state of flaccid atony.

After injury to the cord at any level, the bladder must pass through certain definite stages on its road to recovery; the stage reached depends on the site of the lesion. The progress to recovery can be divided into five stages, namely, (1) the atonic, (2) the autonomous, (3) the hypertonic, (4) the uninhibited reflex and (5) the normal cord bladder. Any actual stage is determined according to four criteria: (1) tonus of the detrusor urinae muscle; (2) optimal storage capacity, together with the presence or the absence of emptying contractions; (3) the amount of residual urine expressed as a percentage of the fill and (4) reflex activity of the external sphincter.

In treatment, the principle of tidal drainage introduced by Munro appears to produce results far superior to anything achieved previously. A siphon and an irrigating apparatus are attached to an indwelling catheter, which periodically fills and empties the bladder to an extent and at a rate corresponding to normal, until activity of the bladder is regained. By this method, reduction of urinary sepsis from 72 to 14 per cent is claimed in cases of injuries to the spinal cord. The disastrous effects of overdistention of the bladder with infected urine are prevented, as well as the later development of a contracted bladder. The apparatus for tidal drainage must be checked from time to time with regard to the volume of fluid entering the bladder and the head of pressure forcing it in so that it can be made to correspond with the progressive stages of recovery. The indwelling catheter should be changed once a week. For men it should be of the whistle tip type. An ordinary self-retaining catheter is adequate for women. Rubber

catheters should be used for both sexes. The whole apparatus should be cleaned once a week. If the bladder is foul, the catheter will need to be cleaned by manual irrigation at intervals until clean enough to avoid intermittent blockade during tidal drainage. In view of Munro's results, it appears imperative to try his methods whenever possible.

Scott [46] states that proper care of the paralyzed bladder is an important part of the management of patients with traumatic myelitis. Early suprapubic cystotomy answers the question of adequate drainage and urinary asepsis more satisfactorily than any other procedure, particularly in the early stages; often it may be the most satisfactory procedure as a permanent method of bladder drainage. The tendency of the paralyzed patient toward the formation of renal calculi should always be kept in mind in these cases.

Rupture.—Beresford-Jones [47] reports a case of spontaneous intraperitoneal rupture of the urinary bladder. The patient was a woman aged 27 years with a sudden pain in the abdomen while walking. The abdomen became distended, and free fluid was found in the peritoneal cavity. Thirty-eight fluidounces (1.1 liters) of urine was withdrawn by catheter. Owing to the fact that catheterization gave positive results on several occasions, the diagnosis of rupture of the bladder was not made. The patient died forty hours after the attack. At necropsy, the abdomen was found to contain 2 pints (1,000 cc.) of fluid. Considerable inflammatory changes were seen on the surface of the intestine. Examination of the bladder disclosed an intraperitoneal rupture on the posterior side.

Inversion.—Micheletti [48] describes an unusual case of total inversion of the bladder, one of the gravest accidents that can befall this organ. Only 14 cases have been found in the literature of the last fifteen years; in 5 of these, inversion was through the urethra and in 9, through a fistula. In Micheletti's case, inversion was through a fistula.

The patient was a woman 68 years of age who at the age of 40 years had suffered vesicovaginal fistula at the time of a severe labor complicated by a third degree laceration of the perineum. She had refused surgical repair for both conditions. Examination revealed a large vesicovaginal fistula, total prolapse of the uterus and the vaginal wall, marked posterior enterocele and partial prolapse of the rectum. Two operative interventions were carried out. The first consisted of repair of the fistula with temporary reduction of the uterine prolapse;

46. Scott, R. T.: Care of Paralyzed Bladder Secondary to Spinal Fractures, Northwest Med. **40**:336-338 (Sept.) 1941.

47. Beresford-Jones, A. B.: A Case of Spontaneous Intraperitoneal Rupture of the Urinary Bladder, Brit. J. Surg. **29**:154-156 (July) 1941.

48. Micheletti, G.: Inversione totale della vescica (contributo patogenetico e clinico), Policlinico (sez. chir.) **47**:481-490 (Dec.) 1940.

the second, performed a month after the first, accomplished restoration of the perineum. The results of both procedures were excellent.

The particular interest in this case lies in the unusual sequence of the evolution of the lesions, which was cystocele, rectocele, prolapse of the uterus and, finally, posterior enterocele. The patient's history revealed that incontinence of urine had developed one week after trauma; prolapse of the rectum appeared two months later. After twelve years, the uterus prolapsed; thirteen years after this there was partial prolapse of the bladder, which reached the state of complete inversion three years later, or twenty-eight years after the original injury.

In observations made on the mechanism of inversion of the bladder, it is worthy of note that the part first involved in the process was either the anterosuperior or the posterosuperior wall and that the last portion of the organ to be exteriorized was the trigone, which suffered inversion much more rarely than the other portions. In Micheletti's case, however, the order of the developments was determined by the twofold circumstance of the serious perineal laceration and the fistula located on Pawlik's triangle, a location so close to the ureteral orifices that the pressure which normally would be exerted by the bladder on the anterior wall of the vagina was markedly reduced. As a result, the weakest point was the posterior vaginal wall; this caused prolapse of the uterus to begin with rectocele at a time when the loss of fat and senile atrophy associated with the menopause had upset the already labile equilibrium between the resistance of the pelvic floor and the intra-abdominal pressure. That inversion had begun with extrusion of the trigone was revealed by the absence of symptoms of urinary retention and the constant presence of two ureteral protuberances which protruded from the fistula.

The mechanism of the formation of this inversion may be likened to that of hernia. The traction of the genital prolapse caused the natural connections of the trigone and the uppermost parts of the vagina to relax. They did this the more easily in view of the presence of the large vesicovaginal defect. After the descent of the vaginal wall, the posterior part of the trigone, having lost its natural adhesions, found an artificial opening, into which it readily engaged. Then, as the traction grew stronger, the supporting apparatus of the bladder became reduced to its lowest terms, until a sudden diminution of abdominal pressure caused the partial inversion to become total.

The complete recovery in this case was the more remarkable in view of the age of the patient and the presence of serious unilateral pyonephrosis. The case is of interest in that it serves to define more precisely the etiology and pathogenesis as well as the clinical picture of inversion of the bladder.

Contraction of Neck of Bladder.—Dillon,[49] in discussing contracted neck of the bladder, states that hyperplasia of the prostate is apparently prevented by early infection and replacement by fibrosis of the submucous prostatic glands. Fibrous ring contractures of the neck of the bladder with hypertrophy of the interureteric ridge follow infection in young adults. Diagnosis is based on nocturia and the degree of angulation of the floor of the bladder with the prostatic urethra as determined by a panendoscope. The presence of trabeculation and hypertrophy of the interureteric ridge with a deep retrigonal pouch is another aid to diagnosis. Best results are obtained by cold steel cutting and light coagulation of the bleeding points. Strong blended tube and spark gap cutting is frequently followed by further fibrosis, which necessitates posterior dilations or further transurethral resection.

HYPOTHYROIDISM AND BLADDER FUNCTION

Sherrill and Mackay [50] discuss hypothyroidism and bladder function and report their findings in an experimental study. Atony of the bladder observed among patients with hypothyroidism stimulated their study of the relation of these conditions in the albino rat. Rats with hypothyroidism regularly revealed evidence of atony of the bladder; this was measured by the filled region, demonstrated by a radiopaque compound, in emptying time of the bladder and lowered ability to sustain an artificial increase in intrabladder pressure.

PROSTATE GLAND

Stone.—Gutierrez [51] reports a series of 29 cases of prostatic calculi; in 17, operation was performed. In treating infection of the lower portion of the urinary tract, it should always be borne in mind that it is possible for calculi to be present within the prostate. Stone is much more common than has been believed, since it runs a symptomless course over a long period and tends to excite inflammation and obstruction slowly. Even when it is found accidentally, the patient should be closely observed because he is harboring latent infection which in the course of time may lead to irreparable damage to the gland, cause abscess, destroy function and, in cases in which the condition is advanced, lead to complete calcification.

Prostatic stone falls into three classes, namely, (1) endogenous, (2) exogenous and (3) endoexogenous, according to the way in which it

49. Dillon, J. R.: Contracted Bladder Neck, a Frequent Result of Youth Delinquency, J. Urol. **46**:510-513 (Sept.) 1941.

50. Sherrill, J. W., and Mackay, E. M.: Hypothyroidism and Bladder Function: An Experimental Study, J. Urol. **46**:34-37 (July) 1941.

51. Gutierrez, R.: Perineal Prostatotomy and Prostatectomy for the Removal of Prostatic Calculi, Ann. Surg. **113**:579-624 (April) 1941.

develops: (1) stone primarily within the substance of the prostate gland as a result of the slow deposit of calcium around the corpora amylacea found normally within the acini and the tubules; (2) stone forming within some part of the upper portion of the urinary tract, later becoming embedded within the region of the prostatic urethra; (3) stone originally forming within the prostate, later coming into contact with exogenous urinary deposits which accelerate the growth of stone so that it becomes prostatourinary calculus. All types may be present in the same case. For treatment, operative removal is demanded when symptoms are produced. At first, the symptoms are insidious and may appear as minor urinary, rectal or genital manifestations of an indefinite nature. As time goes on, they may range from mild frequency and dysuria to total hematuria and complete retention of urine. A few patients complain of urethral stricture. Arthritis or generalized sepsis of long standing was present in some of the cases in the author's series. The association of prostatic calculi with parenchymal prostatitis and adenomatous prostatic hypertrophy is a common occurrence.

Frequently, the diagnosis can be made by rectal palpation, which, in cases in which the condition is advanced, elicits characteristic crepitation and reveals the presence of hard nodules. The presence of these nodules can be confirmed by roentgenograms or urethrocystograms. Cystoscopic examination is helpful, especially if prostatic hypertrophy or characteristic bullous edema is present at the floor of the neck of the bladder and in the region of the prostatic urethra. In 67 per cent of the cases, the diagnosis was made by rectal palpation; roentgen examination was carried out in all cases. It should be emphasized that a urographic examination should not be considered complete that does not include the region of the prostate, since the discovery of clinically unsuspected prostatic calculi by roentgen examination is common.

When operation is indicated, the best surgical treatment appears to be perineal prostatolithotomy. When the condition is associated with adenomatous prostatic hypertrophy, perineal prostatectomy assures permanent cure. Not only should all prostatic stone be removed, but open drainage also should be maintained to relieve infection and restore good function if permanent cure is to be obtained. In 13 of the 17 cases in this series in which operation was performed, the patients were cured, and in 4, they were improved. Of 12 patients who were not operated on but who were treated medically and urologically, 5 were improved, and 7 were not. It appears that endoscopic prostatic resection is not applicable in the majority of these cases, since, as a rule, the stones are multiple. In cases in which prostatitis is a complicating factor, the stones are in closed infected pockets or lie near the capsule in cases of adenomatous prostatic hypertrophy.

Emmett [52] considers the various methods now employed for removal of prostatic calculi, namely, suprapubic prostatectomy, perineal prostatolithotomy, transurethral removal of stone and subtotal perineal prostatectomy, an operation recently described by Henline. Under certain circumstances, each of these procedures seems to possess some advantage. It has been Emmett's experience, however, that the majority of prostatic calculi can be removed satisfactorily by means of transurethral measures. Stone too large to be removed through a cystoscope can be maneuvered into the bladder and crushed with a lithotrite. If, at times, a few fragments are permitted to remain, they usually do not cause symptoms. However, they can be removed at a second operation if desired.

Emmett presents 2 cases of prostatic lithiasis. In 1 of these, the patient was a man 73 years of age who had prostatic enlargement, grade 2. Virtually the entire prostate was filled with calcareous material which was satisfactorily removed by transurethral measures with the use of a McCarthy panendoscope and a Collings knife. The stones were dislodged, maneuvered into the bladder and subsequently crushed with a Bigelow lithotrite. The second case was similar to the first.

Carcinoma.—Because of the frequency of metastasis to the spinal column in malignant disease of the urogenital tract, particularly prostatic carcinoma, the observations of Wolfson, Reznick and Gunther [53] on the early diagnosis of metastasis to the spinal column may be of interest to urologists.

Early involvement of the vertebral bodies which is not demonstrable roentgenographically may be inferred by an increased sedimentation rate, elevated or rising values for serum phosphatase and the type of radicular pain.

This root pain is almost always sharply defined and limited to definite dermatomes, or regions supplied by the nerve roots adjacent to the vertebra or vertebrae involved. It may be confused with the root pain of arthritis; however, there are a number of distinct differences (table). The triad of accelerated erythrocyte sedimentation rate, increase in the level of serum phosphatase and sharply defined regions of spinal nerve root pain is presumptive evidence of malignant metastasis to the spinal column, even in the absence of positive

52. Emmett, J. L.: Transurethral Removal of Large Prostatic Calculi, Proc. Staff Meet., Mayo Clin. **16**:289-293 (May 7) 1941.

53. Wolfson, S. A.; Reznick, S., and Gunther, L.: Early Diagnosis of Malignant Metastases to the Spine: A Clinical Syndrome, J. A. M. A. **116**:1044-1048 (March 15) 1941.

roentgen findings. It is important to recognize this early involvement of vertebrae because adequate roentgen therapy produces dramatic relief of pain and regression of the lesions.

Hyperprostate.—Draper, Slaughter and Denslow,[54] in discussing the effect of testosterone propionate on benign prostatic hypertrophy, state that they did not observe any apparent improvement in the urinary status of their patients which could not be duplicated by the injection of sterile solution of sodium chloride.

Wilhelmi [55] states that most urologists agree that resection is the method of choice in the treatment of all types of glandular obstruction except in cases of adenoma. The indwelling catheter should be omitted whenever possible and supplanted by intermittent catheterization or

Important Differential Findings in Spinal Metastasis and Spinal Osteoarthritis

	Spinal Metastasis	Spinal Osteoarthritis
Distribution of peripheral pain	Usually limited to narrow zones of one or two nerve roots' distribution	Usually covers a large number of spinal dermatomes, with wide areas of distribution
Periodicity and rhythmicity of pain	None; constantly present and intense; relief only by roentgen ray therapy	Influenced by meteorologic conditions; relief by analgesics, vitamin B_1 and physical therapy
Effect of motion on the pain	Aggravates and intensifies the pain; patient shows reluctance to move once a relatively comfortable position is attained	Tends to relieve the pain; patient is constantly turning and changing position because motion affords relief
Deep percussion tenderness	Percussion tenderness over the suspected vertebrae is a constant sign	Percussion tenderness is not present; cutaneous sensitivity may be present
Sedimentation rate	Increased, usually greatly so	Not increased
Serum phosphatase	Increased, or increasing; above 4 Bodansky units	Not increased

suprapubic drainage. Whenever possible, cystoscopy should be followed by immediate operation. The levels of nonprotein nitrogen and urea nitrogen do not necessarily need to be within normal limits before operation if they are stabilized. Ligation of the vas deferens should be compulsory in cases in which the urine is infected and in those in which there is an old history of gonorrhea. Spinal anesthesia administered in small doses is the anesthesia of choice.

The hydrostatic gage is an important accessory in preventing rupture of the bladder or physiologic disturbances from intravesical overdistention. Careful postoperative asepsis with a closed system of

54. Draper, J. W.; Slaughter, G., and Denslow, C.: The Effect of Testosterone Propionate on Benign Prostatic Hypertrophy, J. Urol. **45**:539-547 (April) 1941.

55. Wilhelmi, O. J.: Refinements in Technique Imperative for Successful Transurethral Prostatectomy, J. Urol. **45**:612-621 (April) 1941.

drainage is advocated. Early removal of the indwelling catheter and close scrutiny during the follow-up are suggested.

Polse [56] states that caution should be exercised at all times in doing resection of the prostate. When a patient complains of sudden severe pain in the abdomen while under subarachnoid anesthesia or if extravesical suprapubic distention is suspected, it is advisable to make cystograms immediately. Intensity of the symptoms is usually dependent on the extent and the duration of the extravasation. The treatment for extraperitoneal extravasation is immediate drainage of the bladder and the prevesical space.

Milner and Engster [57] state that in their hands transurethral prostatic resection is the operation of choice in practically all cases of prostatic obstruction. Mortality and morbidity with the attendant economic distress are greatly reduced. Good results depend on resection of all the obstructing tissue and preferably down to the prostatic capsule. If tissue to which the blood supply has been destroyed remains, more marked cystitis with severer symptoms is certain to result after operation. All patients with incontinence should undergo cystoscopic examination, and any tissue impinging within the external sphincter should be resected.

Tuberculosis.—Strom and Thompson [58] report a case of primary tuberculosis of the prostate. They state that tuberculosis of the prostate is seldom recognized and that it is difficult to diagnose clinically. The patient was a man aged 30 years who complained of pain in the left upper quadrant of the abdomen. The urine was normal. He was operated on for cholecystitis with gallstones and died five days later. At necropsy, evidence of tuberculosis in the lungs or the hilar nodes was absent. The kidneys, the ureters and the bladder were grossly normal. A small abscess was found in the center of the left lateral lobe of the prostate. Microscopic evidence of tuberculosis in the lungs, the kidneys or the bladder was absent. The abscess in the prostate revealed the typical microscopic structures of tuberculosis. Tubercle bacilli were demonstrated in the stains, but there was no evidence of tuberculosis in any other part of the body. Strom and Thompson express the belief that this was a case of true primary prostatic tuberculosis of the genital tract.

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56. Polse, M. L.: Extraperitoneal Rupture of the Bladder in Transurethral Prostatectomy, J. Urol. **46**:528-534 (Sept.) 1941.

57. Milner, W. A., and Engster, H. C.: Modern Methods of Handling Prostatic Obstruction: An Evaluation of Transurethral Resection Based on Seven Hundred Cases, J. Urol. **46**:278-282 (Aug.) 1941.

58. Strom, G. W., and Thompson, G. J.: Primary Tuberculosis of the Prostate: Report of a Case, J. Urol. **45**:858-862 (June) 1941.

TESTIS

Tumor.—There has been some speculation [59] as to the lytic properties of the serum of normal pregnant women for chorionic epithelium. It has been reasoned that in many respects the growth of the placenta resembles that of a malignant tumor, that the chorionic villi invade the uterine musculature and that emboli from this invasive tissue are carried to the lungs. Careful examination of the lungs of women who died in childbirth revealed that chorionic emboli were present in 80 per cent of those studied.

However, this invasive tissue fails to grow or produce metastatic tumors, and it is reasoned that there must be some substance in the serum of pregnant women and animals which inhibits this growth and which is lytic for trophoblastic cells and cell emboli. This substance keeps the balance and prevents the chorionic epithelium from running wild. On this basis, it has been suggested that the serum of normal pregnant women be used in the treatment of chorioepithelioma among both men and women.

Twombly and Hocker report the treatment with pregnancy serums of a patient who had chorioepithelioma of the testis with extensive metastasis. Careful urinary assays were made for chorionic gonadotropin, estrogens, androgens and pregnandiol during treatment. Before treatment, the urinary output of chorionic gonadotropin was high, as it usually is in cases of testicular chorioepithelioma; 40,000 to 130,000 mouse units was excreted daily. After the intravenous injection of 250 cc. of serum from the blood of parturient women on two occasions and on another of 250 cc. of serum from blood of the umbilical cord, the urinary output of chorionic gonadotropin increased to as much as 440,000 mouse units daily.

This was not caused by the hormone content of the injected serum, which at most contained only 2,000 to 4,000 mouse units; the observed increase in the urine was 300,000 mouse units. Twombly and Hocker conclude that the increase was caused by nonspecific protein shock.

Urinary estrogenic substances were increased over the values for normal men or menopausal women, and this explains the patient's gynecomastia. The androgenic output was normal, and a crystallized substance was extracted which was thought to be pregnandiol. The serum treatment combined with intensive roentgen therapy had no effect on the progress of the disease, and the patient died.

Epididymitis.—Smith [60] discusses infiltration of the spermatic cord with procaine hydrochloride as treatment for epididymitis. He follows

59. Twombly, G. H., and Hocker, A. F.: Chorioepithelioma in the Male: Treated with Pregnancy Serum, Surg., Gynec. & Obst. **73**:733-739 (Nov.) 1941.

60. Smith, D. R.: Treatment of Epididymitis by Infiltration of Spermatic Cord with Procaine Hydrochloride, J. Urol. **46**:74-76 (July) 1941.

the method of Imbert, who stated that the symptoms associated with acute epididymitis, namely, pain, swelling and redness, are largely caused by a neurovascular disorder and that block of the sympathetic nerves to the testis may relieve pain and bring about rapid cure. Since the sympathetic nerve fibers to the testis and epididymis accompany the vas deferens and the arteries to the testis, interruption of their impulses could easily be obtained by infiltration with procaine hydrochloride. Imbert injected a 1 per cent solution of procaine hydrochloride into the spermatic cord.

In 23 cases of acute epididymitis, the infection was gonorrheal in origin in 15. In most cases the pain was relieved within thirty hours, and the testicular swelling subsided within two weeks. In 8 cases of nonspecific epididymitis, pain disappeared in the majority of cases within twenty hours. The organs were reduced to normal size within about three days. When pain was not relieved within twenty-four hours, reinjection of the cord was carried out. Rarely was a third injection necessary.

During the first five months of 1940, Smith similarly treated 12 patients with acute epididymitis. Eight of these patients had epididymitis of gonorrheal origin. Two obtained complete and permanent relief of pain within seconds after the injection; 4 were relieved of pain within twenty-four hours, and 2 required reinjection the next day. The second injection was followed by complete relief of discomfort.

Three patients had nonspecific epididymitis. The pain of 2 was relieved within twenty-four hours after the injection. The other patient required reinjection twenty-four hours after the first infiltration. This discomfort disappeared forty-eight hours later. In 11 cases, resolution of swelling in the affected epididymis was hastened by this procedure.

Smith uses 10 to 20 cc. of a 1 per cent solution of procaine hydrochloride for infiltration. His technic is as follows: The spermatic cord is picked up with thumb and forefinger above the affected testis, while the overlying scrotal skin is held tense. A no. 22 needle is passed through the skin and, injection being maintained all the while, is advanced through the entire cord. The needle is then partially withdrawn, and by changing its angle in relation to the cord other regions are infiltrated in turn until the entire structure has been injected.

This procedure blocks all periarterial and perivasal sympathetic and sensory nerve fibers so that in a few seconds subjective numbness of the testis occurs, and the organ is painless to pressure. After one or two hours, the numbness of anesthesia disappears, but in cases in which the outlook is most favorable pain or tenderness does not recur. In others, mild degrees of discomfort may return and then disappear on the next day. If pain is still present after twenty-four hours, treatment should be repeated.

TORSION OF THE SPERMATIC CORD

Beare [61] states that torsion of the spermatic cord is relatively common. This would be particularly true if the correct diagnosis were made in all cases. Without a doubt, many cases in which a diagnosis of acute epididymitis, orchitis or strangulated hernia is made are in reality cases of torsion.

It is likely that torsion cannot take place in a spermatic cord and testis which have had normal anatomic development in relation to the surrounding structures. Attachment of the vessels and the mesentery to the lower pole of the testis to form only a narrow band instead of the normally broad one may be a causative factor. The same is true of a large tunica vaginalis attached high on the cord, since this allows too great a range of motion of the testis. Exercise and exertion seem to be part of the immediate cause, but many cases have been reported in which torsion occurred during sleep or when the patient was not exercising.

The onset of pain in the testis is sudden and is soon followed by swelling. According to Cabot, if the patient is a young boy, a history of repeated attacks of testicular pain without urethritis or urinary infection is almost diagnostic of torsion of the cord. Vomiting, a mild degree of shock and elevation of temperature may or may not accompany the attack. The testicular mass will usually be high in the scrotum, and the epididymis will be anterior or lateral to the testis instead of in the normal posteromedial relation. Elevation of the testis will increase the discomfort. The condition occurs as often on the left as on the right side. There are two types, intravaginal and extravaginal, according to whether torsion occurs within or without the tunica vaginalis.

In the majority of cases the best treatment is open operation. If the testis and cord are found to be viable, it may be possible to untwist the cord and suture the testis and cord to the scrotal wall so that torsion cannot recur. If the testis and cord are necrotic, orchidectomy is the procedure of choice. Some physicians favor manual detorsion without opening the scrotum, but in most cases this is impossible, and valuable time is lost in the attempt. In cases of recurring torsion, if the twist is not severe enough to produce gangrene immediately, chances for preserving the testis are best. This is true also in cases of acute torsion, if the condition is recognized and operation is performed immediately.

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61. Beare, J. B.: Torsion of the Spermatic Cord: Report of Case, Proc. Staff Meet., Mayo Clin. **16**:430-432 (July 2) 1941.

HYDROCELE OF THE CANAL OF NUCK

Counseller and Black[62] state that hydrocele of the canal of Nuck is encountered only rarely. They report 17 cases.

Hydrocele or cystic tumor which accompanies the round ligaments through the inguinal canal of women is the exact counterpart of encysted hydrocele of the cord of males and results from the accumulation of fluid in a persisting diverticulum of Nuck, which corresponds to the vaginal process of the peritoneum in the male. In keeping with this concept of its origin, the cyst is usually found accompanying the round ligament but not originating within it. It is lined with a pavement epithelium similar in all respects to the cells lining the peritoneal cavity. The wall of the hydrocele is made up chiefly of fibrous tissue with a single layer of flattened cells on the inner surface. Smooth muscle may be present in the wall, but this finding is not constant. The most important problem presented by the condition is the differential diagnosis, chiefly from hernia. A careful history should serve to distinguish hydrocele from vulvovaginal cysts.

In the 17 cases from the Mayo Clinic, the differential diagnosis between hernia and hydrocele in female patients was difficult. In most cases, rather small tumors were so well confined to the inguinal canal that they could not be palpated readily. Many of the hydroceles were associated with hernia, and this complicated the questions of whether the mass could be reduced and whether there was an impulse on coughing. In some cases, the cysts were small enough to be freely movable and to be forced toward the subcutaneous inguinal ring when the patient stood or strained. In virtually all such cases the findings indicated to the examiner the presence of a reducible hernia.

In cases in which the hydrocele had extended beyond the subcutaneous inguinal ring toward the vulva, the findings were more diagnostic. Palpation was much facilitated, and the mass could be transilluminated. It was also evident that the tumor could not be reduced completely and that it was not an incarcerated hernia.

The oldest patient in the series of 17 was aged 51 years, and the youngest, 28. The average age at the time of operation was 37. In none of the patients had the hydrocele been noted during childhood, and the earliest age at which any patient noticed symptoms was 20 years. The average duration of symptoms was nineteen months. The longest time that a mass had been noticed was sixteen years, and the shortest, two weeks. The duration of the mass, as noticed by the patient, had no relation to its size. Thus, the patient who had the tumor for sixteen years had a hydrocele the size of a plum (about 5 cm. in

62. Counseller, V. S., and Black, B. M.: Hydrocele of the Canal of Nuck: Report of Seventeen Cases, Ann. Surg. **113**:625-630 (April) 1941.

diameter) which had not increased perceptibly in size throughout this time. The largest hydrocele had been noted for thirty months and during this time had increased slowly in size.

GENITAL TUBERCULOSIS

Hammond,[63] after examining a large number of patients, expresses the view that tuberculosis of the genital tract is a definite entity. Before reaching a diagnosis, cystoscopy must always be carried out. If the urine contains tubercle bacilli and pus, each kidney must be catheterized separately. Tuberculous disease may arise anywhere in the genital tract. The course is chronic, and the symptoms are few. In more than 50 per cent of Hammond's cases, there was roentgen evidence of tuberculous lesions in the lungs. The disease may begin either in the globus major or the globus minor; usually it starts in the latter. At times, especially in cases in which the disease begins acutely, it may involve the entire epididymis at the start and extend along the vas deferens, the lesions being most extensive in the proximal and distal thirds. Sometimes it is associated with marked fibrosis; this has a tendency to contract and thus lead to nodulation or beading of the vas deferens and ultimately to its obliteration—the reason why azoospermia is so frequent. The lesions in the seminal vesicle and the prostate are found at first on the same side as the disease in the testis, and generally those in the vesicle arise before those in the prostate. Later, the opposite vesicle and lobe of the prostate become involved. When this has happened, it is likely that the other testis will be affected. In cases in which the condition is advanced, both testes are involved in 40 per cent. When the prostate is diseased, miliary tubercles and ulcers may be present in the prostatic urethra. Fibrosis may cause narrowing of the urethra; sooner or later it gives rise to back pressure on the kidneys and symptoms of uremia may arise.

Genital tuberculosis runs rather a chronic course with little tendency to dissemination other than in the genital tract. It is characterized by fibrosis rather than by suppuration. It is probable that the bacilli reach the testis by way of the blood stream, that they are taken up by the cells and pass through the seminiferous tubules into the ejaculatory duct; the first lesion is likely to be found where this duct joins the vas deferens. It is possible, however, for the disease to begin in two places in the genital tract at the same time.

The disease occurs in most cases when the patient is between the ages of 20 and 40 years; it rarely occurs in persons under 20. The oldest patient was a man aged 60 years. Generally, the patient presents

63. Hammond, T. E.: Genital Tuberculosis in the Male, Brit. J. Urol. **13**: 43-73 (June) 1941.

himself because he has noticed a swelling of the testis. To reach a diagnosis, the physician generally has to be guided by the course which the disease runs. If the swelling is attributable to tuberculosis, it becomes a hard craggy mass that is definitely related to the epididymis. Formation of abscess has been the exception in cases of acute disease. The swelling is generally painless. A characteristic feature is the absence of tenderness and the development of a cold abscess without signs of inflammation. Hydrocele developed in less than 20 per cent of the cases. In only 30 per cent were bacilli found in the urine. Examination of the prostatic urethra with a posterior urethroscope at times revealed miliary tubercles and superficial ulceration.

Treatment in a sanatorium is just as essential for this as for tuberculous disease elsewhere in the body, and epididymectomy or orchidectomy does not in any way remove the necessity of it. It is doubtful whether either of these operations gives better results than those that follow treatment in a sanatorium with division of the vas deferens. The desirability of ligature of the opposite vas as a means of preventing the disease from spreading to the other testis is debatable. New tuberculin is administered every five days, starting with 0.0001 mg. and increasing slowly to 0.001 mg. It should be continued for at least a year after the patient has left the sanatorium. Gold salts are useful if there is much proliferation. The prognosis is that of tuberculosis in general. If the disease does not subside, orchidectomy should be performed. The outlook is dependent on many outside factors.

GONORRHEAL URETHRITIS

Boslow [64] discusses the treatment of gonorrhea with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole). This treatment is found to have less toxic effect, and it is demonstrated that sulfathiazole is more rapidly and uniformly absorbed but more rapidly excreted than sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). Boslow reviews a series of 58 cases of acute gonorrhea. In none of these cases had previous chemotherapy been given. All patients were hospitalized throughout the course of the treatment.

On admission, each patient was given an initial dose of 4 to 5 Gm. of sulfathiazole and then 1 Gm. every four hours for twenty-four hours. The dose was then reduced to 0.66 Gm. every four hours for forty-eight hours. After this period, 0.5 Gm. was given every four hours for ten to twelve days. It was thought advisable to give a large initial dose to avoid the possibility of the formation of sulfathiazole-resistant strains which have been shown to exist in vitro with related compounds. The

64. Boslow, H. M.: Treatment of Gonorrhea with Sulfathiazole, Mil. Surgeon **88**:659-660 (June) 1941.

drug was given for two weeks, since positive smears and cultures could frequently be shown to exist for several days after the cessation of discharge. Of the 58 patients treated, all but 5 were clinically cured—a cure rate of 91.5 per cent.

There were only three reactions in this series. One consisted of transient headache of twenty-four hours' duration; one was conjunctivitis which lasted for three days, and in 1 case nausea and vomiting occurred on the eleventh day of treatment. The hemoglobin value and the number of leukocytes and erythrocytes disclosed no depressant effect whatever throughout the treatment. No complications developed while patients were undergoing treatment.

Pelouze,[65] in discussing gonorrhea in male patients, states that sulfanilamide does one of three things for and to patients with gonorrhea: It cures some; it makes symptomless carriers of some, and it fails to have any influence whatever on others. The apparent cure rate obtained with it is so low in comparison with the cure rates achieved with sulfapyridine and sulfathiazole that many careful clinicians are convinced that it is better not to use it for this disease. The cure rate among ambulatory patients is not more than 30 per cent. The toxicity rate is at least 50 per cent. Sulfapyridine, dose for dose, is about as toxic as sulfanilamide; the apparent cure rate is from two and a half to three times greater, and it has the attraction of making few symptomless carriers. Sulfathiazole is unquestionably the best drug of the three for the treatment of gonorrhea by reason of the far lower toxicity rate. The therapeutic value is in every way equal to that of sulfapyridine.

In discussing the highly important question of carriers, Pelouze states that although they still harbor gonococcus and can transmit it to others, they have absolutely no symptoms to suggest its presence. Usually, they can indulge without the slightest return of symptoms in all of those activities that were so potent in the production of symptoms in cases of latent gonorrhea in the old days before sulfanilamide therapy. When they transmit the disease to others, most, if not all, of their victims become totally asymptomatic carriers. They have not the slightest reason to suspect that they have been infected, although careful microscopic or cultural studies will reveal the presence of the gonococcus. When one of these secondarily infected persons transmits the infection to a third person, the latter is left in no doubt, for he has a frank attack of the disease. Socially, these primary and secondary carriers are the greatest present day therapeutic concern. Physicians are not fooled by those who fail to benefit from treatment but can be unmercifully deceived by those who still have the disease but do not present clinical evidences of it.

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65. Pelouze, P. S.: Gonorrhea in the Male: Modern Treatment, J. Michigan M. Soc. **40**:444-448 (June) 1941.

High concentrations of sulfanilamide and its derivatives in the blood are not needed in the treatment of urogenital gonorrhea. Some of the greatest successes have been achieved in cases in which the concentration of the drug used was not more than 1.5 mg. per hundred cubic centimeters of blood. Some failures occurred when the concentration was 15 mg. If sulfanilamide or one of its derivatives is acting favorably, the patient should be entirely free of symptoms by the end of the fifth day. If this does not occur, he can be classed as a definite failure with regard to the drug used, and medication with that particular drug should be discontinued. Then after a few days' rest, the patient should be given another drug; failing of benefit from this, he should be given local treatment.

Conditions which fail to respond to sulfanilamide commonly are favorably influenced by sulfathiazole and sulfapyridine, but the converse is not true. Sulfathiazole commonly acts favorably when sulfapyridine fails. The present custom is to discontinue the administration of sulfanilamide and its derivatives after a week or ten days. There is nothing to suggest that longer medication is needed or of value.

There are many useful schemes of dosage, none of which aim at high concentrations in the blood. The following dosages have been employed by different careful clinicians with about equal curative results:

Days	1	2	3	4	5	6	7	8	9	10
Grams	3	3	3	3	3	3	3			
Grams	4	3	3	2	2	2	2	2	2	2
Grams	3	3	2	2	2	2	2	2	2	2

With these dosages and shortened periods of administration, the toxic factors are at a low ebb; with sulfathiazole they are almost nil.

As a criterion of cure, persistently clear urine for two weeks or longer is of little value. At least 1 out of every 3 patients treated with sulfanilamide and showing this sign is still infected.

By the use of better drugs it is obvious that it is possible to eradicate quickly most gonococcic infection if patients can be kept under treatment for the required length of time. Not only should this be done, but a much longer period of observation should be insisted on after seeming cure than has been generally demanded.

Uhle, Latowsky and Knight[66] state that sulfapyridine and sulfathiazole are equally efficacious in the treatment of gonorrheal urethritis in male patients. Toxicity is manifested less after treatment with sulfathiazole than after the use of sulfapyridine. Sulfathiazole is the drug of choice for the treatment of gonorrhea. It would seem that a

66. Uhle, C. A. W.; Latowsky, L. W., and Knight, F.: Gonorrheal Urethritis in the Male: Treatment with Sulfapyridine and Sulfathiazole, J. A. M. A. **117**:247-249 (July 26) 1941.

combination of oral chemotherapy and local treatment is preferable. Chemotherapy has altered the conceptions of the provocative tests. The value of the culture over the smear in pronouncing a patient cured should be stressed. A social menace is created by the asymptomatic carrier.

A review of the literature [67] reveals that cases of proved gonococcic pyelonephritis are rare. According to the criteria laid down by Johnson and Hill, only 17 cases have been reported. May reports a case of gonococcic pyelonephritis associated with tuberculosis in the same kidney, bringing the number of cases to 18. Apparently, this is the first report of the occurrence of gonococcic and tuberculous infection in the same kidney.

Proof of the gonococcic nature of the infection was based on the morphologic appearance of the organism found in the renal urine and in pus from the specimen, on the cultural characteristics, including a positive oxidase reaction, on two positive complement fixation reactions, which became negative eleven days after nephrectomy, and on the pathologic findings in the specimen. According to Todd and Sanford, a positive complement fixation reaction is definite evidence of gonococcic infection, and a positive oxidase reaction of colonies which on subculture are found to be growths of gram-negative diplococci is absolute identification of the gonococcus.

Since the criteria for diagnosis were established by Johnson and Hill, improved methods of culture and the oxidase reaction have been introduced. These provide additional means of identifying gonococcus.

The symptoms and the clinical findings of gonococcic pyelonephritis are discussed briefly. It is probable that gonococcic pyelonephritis occurs in many cases of gonorrheal infection of the lower portion of the urinary tract and either subsides spontaneously or reacts favorably to treatment for infection of the lower portion of the urinary tract. The fact that in most of the reported cases the condition was unilateral implies that the infection may become chronic only in a kidney made vulnerable to gonococcic attack by some underlying abnormality, usually of an obstructive nature.

Treatment in most of the reported cases of proved gonococcic pyelonephritis, as it was in this case, has been nephrectomy. Sulfanilamide in the dosage of 45 grains (2.91 Gm.) a day for forty-four days, a total of 1,980 grains (128.04 Gm.) was without effect, possibly because of other infection and the extent of the damage to the kidney. Nevertheless, it is believed that rigorous sulfanilamide therapy should be given a trial before more radical treatment is undertaken.

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67. May, J. A.: Gonococcal Pyelonephritis: A Complication of Renal Tuberculosis, J. Urol. **46**:535-541 (Sept.) 1941.

UROLOGIC OPERATIONS

Priestley, Walters and Counseller,[68] in discussing urologic operations at the Mayo Clinic during 1939 and 1940, state that the general mortality rate of 1.4 per cent for all urologic operations during 1939 was the lowest ever obtained at the clinic. During 1940, the mortality rate of 2.1 per cent, although higher than that during 1939, was still below the average of preceding years.

Of the various lesions for which operations were performed on the kidney, nephrolithiasis was the most frequent. The hospital mortality rate of approximately 0.5 per cent in 180 cases of renal calculi for 1939 was less than average, while the rate of 4.2 per cent for 1940 was higher than usual. From a surgical viewpoint, discriminative use of nephrostomy not only has reduced the risk of operation but also has improved ultimate results. During the last two years, nephrectomy has been required in 28 to 30 per cent of the operations performed for renal calculi. If more patients with nephrolithiasis were seen earlier during the course of the disease and prior to extensive renal damage, this incidence of nephrectomy could be materially reduced. In general, it has been the experience of Priestley, Walters and Counseller that a renal calculus which is too large to be passed spontaneously and which is lying free in the pelvis or in one of the calices, even though it has caused little renal damage and has resulted in few clinical symptoms, should be removed surgically. If operation is deferred, symptoms usually become more severe and renal damage more extensive—factors which increase the possibility that nephrectomy rather than a conservative operation will be required subsequently. For these reasons, early surgical treatment for nephrolithiasis, as for many other conditions, is preferable. Pelviolithotomy is performed in approximately 50 per cent of all cases of nephrolithiasis, and in approximately 20 per cent of cases nephrolithotomy is required. Nephrostomy, in the surgical management of renal stone, has its greatest usefulness in the presence of long-standing obstruction, excessive infection and extensive renal damage when nephrolithotomy is performed.

Fifty-four patients with staghorn calculi were treated surgically during 1939 and 1940, with 1 death. In 8 of the cases, bilateral stones were present. Conservative operations were performed on 36 kidneys.

In the treatment of hydronephrosis, conservative operations continue to give satisfactory results in many instances. Resection of the renal pelvis and reimplantation of the ureter into the dependent portion of the renal pelvis have proved satisfactory in cases of large hydronephrosis. The use of soft rubber splinting catheters and adequate drainage by

68. Priestley, J. T.; Walters, W., and Counseller, V. S.: Report of Urologic Surgery for 1939 and 1940, Proc. Staff Meet., Mayo Clin. **16**:625-630 (Oct. 1) 1941.

nephrostomy have demonstrated their value on repeated occasions in cases of this type.

Sixty-five patients submitted to operations performed for lesions of the ureter; there was 1 death. Most of these operations were performed for ureterolithiasis. During this same interval, 88 manipulations for ureterolithiasis were performed on 83 patients without death.

During 1939, 70 suprapubic operations on the bladder were performed, with 7 deaths; during 1940, 63 similar operations were performed, with 6 deaths. Many of these operations were performed for neoplastic lesions, and in many cases the patients were in poor condition. Continued development of transurethral procedures greatly reduces the number of indications for suprapubic surgical treatment of vesical lesions. It is felt, however, that total cystectomy could well be used more frequently for carcinoma of the bladder. During 1939 and 1940, total cystectomy was performed for carcinoma of the bladder on 10 patients, with 2 deaths. When total cystectomy is performed in properly selected cases, there is every reason to anticipate that ultimate results will be satisfactory. Although the indications for this operation cannot be dogmatically stated at this time, it is believed that total cystectomy can be employed to advantage in four main types of cases, namely, cases of (1) extensive low grade lesions, (2) low grade lesions of multicentric foci of origin comparable to multiple polyposis of the colon, (3) repeatedly recurring low grade lesions and (4) high grade lesions which, to the best of knowledge, are still confined to the bladder. Some satisfactory immediate results have been obtained during recent years from total cystectomy; it is anticipated that ultimate results may prove to be equally favorable.

During 1939, only 9 suprapubic operations were performed for lesions of the prostate in contrast to 1,000 transurethral resections performed during the same period for benign or malignant prostatic enlargement. During 1940, operations were performed on 60 patients for congenital abnormality of the genital tract, including cryptorchidism, hypospadias and epispadias.

PEYRONIE'S DISEASE

Beach [69] appeals for universal recognition and sympathetic treatment of Peyronie's disease. He believes that the rarity expressed by statistics is unsubstantiated by diagnostic accuracy, and he details differential diagnoses. Clinical data on 12 patients under observation and treatment for at least nine months are presented. Painful deflected erections are frequently accompanied by conspicuous psychic trends, symptoms corresponding to the degree, the type and the extent of the

69. Beach, E. W.: Peyronie's Disease or Fibrous Cavernositis: Some Observations, California & West. Med. **55**:7-10 (July) 1941.

morbid deviation. Pathognomonic of the disease is an indurated saddle-shaped plaque with well defined edges tightly adherent to Buck's fascia. Fibrous thickening is usually limited to the dorsum; the plaques involve only the septum and/or the tunica albuginea. In most of Beach's cases, localization was in the midline or behind the caput rather than at the base. Hard fibromatous or keloid-like acellular tissue was encountered in the 3 cases in which operation was performed, but inflammatory reaction, implication of the corpus spongiosum, calcific deposits or cartilaginous, osteochondrous or osseous metaplasia were absent. Prognosis should be guarded, as the onset is insidious; its course is unpredictable, and spontaneous regressions are common.

Beach discredits the phylogenetic hypothesis of os priapi but grants certain causative significance to the nobelian bones of the ascaphus, and he illustrates the architectural dissimilarity between the phalli of seals and men and the common anatomic distribution of sclerotic plaques. Incidence of the disease in the fifth and sixth decades suggests a causal relation between retrograde changes of senescence and fibrous cavernositis. Treatment of concomitant pathologic lesions as well as medical fibrolytic therapy is unavailing. Diathermy and irradiation have merits; operation should be highly selective and plastic.

NECROTIC PAPILLITIS

Mellgren and Redell [70] report 2 cases of necrotic papillitis associated with chronic pyelonephritis. In 1 case signs of urinary stasis (hypertrophy of the prostate) were present. An amyloid-like substance was found in the renal papillae in both cases. This amyloid degeneration was regarded as a predisposing factor in the production of papillary necrosis. The pathologic changes present in cases of necrotic papillitis correspond to a definite clinical picture. In most cases the clinical diagnosis is made by roentgen examination.

EFFECT OF ESTROGEN ON TESTICULAR FUNCTION

Heckel and Steinmetz [71] discuss the effect of estrogen on the function of the human testis. They report several cases in which intramuscular injections of alpha estradiol benzoate were given. In all cases there was marked reduction in the total number of spermatozoa. The other effects on these patients were gradual enlargement and hypertrophy of the breast and a gradual loss of libido; none of the patients, however, became completely impotent.

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70. Mellgren, J., and Redell, G.: Zur Pathologie und Klinik der Papillitis necroticans renalis, Acta chir. Scandinav. **84**:439-457, 1941.

71. Heckel, N. J., and Steinmetz, C. R.: The Effect of Female Sex Hormone on the Function of the Human Testis, J. Urol. **46**:319-321 (Aug.) 1941.

SULFANILAMIDE THERAPY

Thompson, Herrell and Brown [72] report a case in which anuria occurred after treatment with sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine). On the basis of their experience, it does not appear that sulfadiazine is a drug completely without toxic properties. It is their opinion that the administration of sulfadiazine may be followed by any of the reactions commonly experienced with chemotherapeutic agents which contain the radical of the parent compound, but they believe that sulfadiazine causes less gastrointestinal irritation (nausea and vomiting) than other derivatives of sulfanilamide. Headache, drug fever, dermatitis and leukopenia have been experienced with equal frequency after the administration of this compound.

The authors state that several facts of importance have arisen from the development of anuria in their case. The urinary output of patients receiving chemotherapy should be maintained between 1,200 and 1,500 cc. per day. The formation of crystals will occur as frequently after the administration of this compound as after the administration of either sulfapyridine or sulfathiazole, if the same precautions concerning urinary output are not taken. Acidity of the urine does not appear to be of great significance in the acetylation of this compound. No question of the possible therapeutic effectiveness of sulfadiazine is raised, but grave question is made of the common belief that the compound is relatively safe. The same fundamental principles apply to the administration of this compound as to the administration of the other two compounds which have a similar action, namely, sulfapyridine and sulfathiazole.

Donahue,[73] in a discussion of the use of sulfanilamide in genitourinary wounds, reports 4 cases in which suprapubic prostatectomy was performed for purulent residual urine. With the use of sulfanilamide, the wounds healed by primary intention except for the region occupied by the suprapubic drains. Two of these patients were obese and had thick fatty abdominal walls. In every instance, wounds left by cystotomy likewise healed by primary intention. Sulfanilamide was used also after incision and drainage of a perirenal abscess, the postoperative drainage continuing only a short time. The wound around the drain closed by primary intention.

In conclusion, Donahue states that sulfanilamide powder has proved to be of value in the healing of wounds and may be used without fear of damage to tissue. Further experimental work must be done to determine the minimal effective amounts of sulfanilamide.

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72. Thompson, G. J.; Herrell, W. E., and Brown, A. E.: Anuria After Sulfadiazine Therapy, Proc. Staff Meet., Mayo Clin. **16**:609-612 (Sept. 24) 1941.

73. Donahue, C. D.: The Use of Powdered Sulfanilamide in Infected Genitourinary Wounds, J. Urol. **46**:562-566 (Sept.) 1941.

Latowsky, Baker, Knight and Uhle [74] present a study of sulfadiazine in the treatment of gonorrheal urethritis in men. A total of 57 patients were studied, 55 of whom were followed to the completion of the study. Of the 55 patients followed, 93 per cent were cured after an average of eight days of treatment with an average dose of 17.5 Gm. Toxic reactions occurred in only 8.8 per cent of the cases. The average time elapsing before the cultures first became negative for gonococci was thirteen days. The criteria of cure in this study were strict and included as the final provocative test two or more negative smears and cultures of the prostatic fluid.

Neter [75] states that sulfadiazine has bacteriostatic and bactericidal properties toward Bacillus coli isolated from patients with infection of the urinary tract. In a concentration of 100 mg. per hundred cubic centimeters of blood, it was found to be less effective than sulfathiazole, somewhat more effective than sulfanilamide and sulfanilylguanidine and approximately equally as effective as sulfapyridine.

Sulfadiazine had definite bactericidal activity toward B. coli in urine. It exerted greater killing power in urine than in mediums that either are favorable for growth (broth) or do not support visible growth of the organisms (phosphate buffer solution).

A patient who had pyelitis due to B. coli and enterococcus and who was treated unsuccessfully with adequate doses of sulfanilamide was promptly cured by the administration of sulfadiazine.

Sulfadiazine exerts some bacteriostatic activity toward enterococci isolated from patients with infection of the urinary tract. Toward certain strains it is less effective than equal concentrations (100 mg. per hundred cubic centimeters of blood) of sulfathiazole.

Satterthwaite, Hill and Young [76] present an analysis of 155 cases of urologic disease in which sulfadiazine was given. The toxicity of sulfadiazine is low. In only 14 of this series of 155 cases was any reaction to the drug observed, and in each case this sensitivity was minimal and quickly disappeared when administration of the drug was stopped. Further, these were all surface reactions and easily observed. Partial reduction in the urinary output, severe leukopenia or anemia did not occur. This is in marked contrast to the action of other derivatives of sulfanilamide.

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74. Latowsky, L. W.; Baker, R. B.; Knight, F., and Uhle, C. A. W.: The Treatment of Gonorrheal Urethritis in the Male with Sulfadiazine: An Analysis of Fifty-Seven Cases, J. Urol. **46**:89-94 (July) 1941.

75. Neter, E.: The Antibacterial Activity of Sulfathiazole Toward B. Coli and Enterococci Isolated from Patients with Infections of the Urinary Tract, J. Urol. **46**:95-100 (July) 1941.

76. Satterthwaite, R. W.; Hill, J. H., and Young, H. H.: The Use of Sulfadiazine in Urinary Tract Infections and Gonorrhea and as a Prophylactic to Prevent Postoperative Infections, J. Urol. **46**:101-109 (July) 1941.

Forty-four patients with infection of the urinary tract received the drug. Sulfadiazine was found to be efficacious in vivo against Proteus vulgaris, Pseudomonas pyocyanea, Escherichia coli, Aerobacter aerogenes and, to a lesser extent, Staphylococcus albus. In a series of 14 cases in which operation on the urinary tract had not been performed recently, all but 3 were cleared of their infection.

Fifty cases of gonococcic urethritis were analyzed. Of 30 patients who returned for observation, only 4 failed to respond to sulfadiazine therapy, 86 per cent having negative prostatic cultures and no evidence of any recurrence. These results were obtained with a minimum of toxic reactions. Sulfadiazine offers great promise in the treatment of gonococcic urethritis.

The use of sulfadiazine to prevent or to reduce postoperative complications in cases of urologic disease appears to be successful. In a series of 64 cases in which the patients were treated either before operation or both before and after with sulfadiazine, there has been only a single instance of transitory bacteremia.

Helmholz [77] states that according to observations in vitro sulfathiazole is definitely superior to sulfanilamide as a urinary antiseptic in concentrations of 10 to 30 mg. per hundred cubic centimeters of urine. The bactericidal action of sulfathiazole in concentrations of 10 mg. per hundred cubic centimeters of urine brings it well within the range possible for therapeutic use for urinary infection in cases in which the kidneys are badly damaged. From Helmholz' experience, the doses used in these cases were too large, and doses of 0.3 to 0.65 Gm. (5 to 10 grains) per day deserve a trial.

METHENAMINE MANDELATE AS A URINARY ANTISEPTIC

Kirwin and Bridges [78] report their findings in a clinical investigation of the urinary antiseptic methenamine mandelate. They state that although mandelic acid and methenamine have both been used extensively as urinary antiseptics, their toxic effects, particularly after long-continued administration, have seriously limited their employment.

The chemical combination of these two drugs having been found practical, the authors made use of methenamine mandelate in the treatment of a group of patients. In 63 cases in which full data were available, excellent results were obtained. An average dosage of three

77. Helmholz, H. F.: A Comparison of the Bactericidal Effect of Low Concentrations of Sulfanilamide and Sulfathiazole on Bacteria from Urinary Infections, J. Urol. **46**:322-331 (Aug.) 1941.

78. Kirwin, T. J., and Bridges, J. P.: Studies in Urinary Antisepsis: Clinical Investigation of Mandelamine, a Recently Introduced Urinary Antiseptic, Am. J. Surg. **52**:477-480 (June) 1941.

tablets, each consisting of 0.25 Gm. of methenamine mandelate, given three times daily, readily controlled most of the common urinary infections and maintained a urinary acidity below *p*H 6.0 without the use of any accessory administration of acid. In the majority of cases the urine cleared within three to five days, and such symptoms as frequency and urgency of urination were reduced or entirely eliminated.

None of the patients manifested toxic symptoms at any time. This demonstrated that the effectiveness of methenamine as a urinary antiseptic has not been impaired by its chemical combination with mandelic acid, although nausea, vomiting and other gastrointestinal disturbances induced by large doses of mandelic acid have been eliminated.

ENURESIS

Spence,[79] in discussing enuresis, states that there should be a general sizing-up of the patient by a pediatrician and a brief period of conservative medical treatment. If this regimen is unsuccessful or if at any time pyuria, hematuria, fever or any other symptoms suggestive of genitourinary disease are present, there should be a thorough investigation by a urologist. Major disease will thus be detected and appropriate treatment carried out.

In the majority of cases of refractory enuresis in girls, chronic granular urethritis will be found to be the basis and its response to treatment is most gratifying. The necessary dilations can be carried out easily by either the urologist or the pediatrician. In boys with refractory enuresis, after major disease and pinpoint meatus are excluded, dilation and instillation are satisfactory.

PREVENTION OF POSTOPERATIVE URINARY RETENTION

Helfert and Granet [80] discuss the prevention of acute urinary retention following anorectal and perineal surgical procedures. In 140 cases in which anorectal or perineal urologic operative procedures were performed, 30 cc. of a 0.5 per cent aqueous solution of mercurochrome was instilled into the urinary bladder on completion of the operation. Acute urinary retention requiring catheterization occurred in only 1 case (0.8 per cent). In a previous series of 100 similar cases in which mercurochrome was not used, acute urinary retention requiring catheterization occurred in 57.

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79. Spence, H. M.: Urologic Aspects of Enuresis, South M. J. **34**:830-833 (Aug.) 1941.

80. Helfert, I., and Granet, E.: Prevention of Acute Urinary Retention Following Anorectal and Perineal Surgical Procedures, Am. J. Surg. **53**:129-130 (July) 1941.

URINARY SYMPTOMS IN GYNECOLOGIC DISEASE

Hochman,[81] in a review of 500 gynecologic patients with urinary symptoms, states that urinary symptoms in the great majority of cases have their origin in the vesicourethral junction. In such cases, meticulous examination of the urethra, the neck of the bladder and the bladder should be carried out.

Correction of gynecologic disease and abnormal physiologic changes is frequently followed by alleviation of urologic symptoms. Consideration of the patient's history, particularly in regard to menopause, marital status, mental health, age and other factors, is important in deciding on treatment. Dilation of the urethra is of definite value in the treatment of diseases of the vesicourethral junction. Hydrotherapy, general hygienic measures and proper sedation should accompany local treatment. The term "cystitis," so frequently used as a diagnosis to cover urinary symptoms, should be replaced by a term applicable to the specific pathologic process found. The gynecologist should have proper training in cystoscopy and endoscopy of the urethra.

URACHAL STONE

Dreyfuss and Fliess[82] report a case of patent urachus with the formation of stone. The patient, a girl aged 11 years, died shortly after entering the hospital. At the age of 5 years she had had pyuria and had passed stone. Later, she had shown evidence of cystitis and pyelonephritis. Shortly before entering the hospital, she became desperately ill and had convulsions. The urine contained pus and albumin, and the number of leukocytes was increased. At necropsy, the urinary bladder was found to be large and thickened. It extended up the umbilicus, and its fundus was adherent to it. The ureteral openings were hidden by folds of edematous mucosa but were patent. A light brown stone, 4 cm. long and 1.8 cm. wide, was firmly lodged in the upper segment. The stone consisted of uric acid. The final anatomic diagnosis was persistent fetal bladder with severe inflammation and formation of stone.

CHANGES IN THE PHYSICAL PROPERTIES OF SEMEN

Hotchkiss[83] states that there were wide variations in the volume, the number of cells and the motility of the spermatozoa in 642 specimens

81. Hochman, S.: A Review of Five Hundred Gynecological Patients with Urinary Symptoms, Am. J. Surg. **52**:472-476 (June) 1941.

82. Dreyfuss, M. L., and Fliess, M. M.: Patent Urachus with Stone Formation, J. Urol. **46**:77-81 (July) 1941.

83. Hotchkiss, R. S.: Factors in Stability and Variability of Semen Specimens: Observations on Six Hundred and Forty Successive Samples from Twenty-Three Men, J. Urol. **45**:875-888 (June) 1941.

of semen submitted by 22 men. The morphologic types exhibited relatively less fluctuation than did the other three characteristics of the semen. The viscosity of seminal specimens varies considerably.

Frequent coitus tends to reduce the volume and the number of cells without materially altering the motility and the appearance of spermatozoa. Sexual abstinence for seventy-two hours promotes uniformity of specimens but does not eliminate wide variations that can be explained by losses in collection of the specimen, laboratory errors or minor alteration in health and habits. Men tend to hold to certain levels from which deviations take place. The clinical importance of such fluctuations is particularly significant in marginal specimens. Illness may have an adverse effect on semen, which is most marked about thirty days after the disturbance in health. Recovery takes place at a slightly slower rate.

OPERATION ON THE VENA CAVA

Hyman and Leiter [84] report a series of 11 surgical procedures on the vena cava. Experimental and surgical procedures have demonstrated that complete ligation of the vena cava below the renal veins is compatible with life. In 4 cases of this series, the vena cava was accidentally injured, while in the other 7 cases surgical operation was deliberate. The deliberate type of operation on the vena cava is generally associated with renal neoplasms or adherent pyonephrotic kidneys. With the newer sulfanilamide preparations in general use, the indications for operation on the vena cava in inflammatory conditions will be reduced to a minimum. Death occurred postoperatively in 3 of the 11 cases. The authors stress that the renal vein and the vena cava should always be explored in cases of right renal neoplasm. For this reason, a wide exposure, necessitating resection of one or two ribs, is advisable. In some of the cases reported, the patient survived a three year period during which thrombi were present in the vena cava. The presence of a tumor thrombus in the vena cava, while certainly grave, does not necessarily imply an immediately fatal course.

APPENDICAL CALCULUS

Guido [85] reports a case of appendical calculus which simulated ureteral calculus both in the roentgenograms and in the symptoms.

He states that true calculus of the appendix is always visible roentgenographically but that because of its rarity, the shadow is usually mistaken for ureteral calculus. Commonly, the ureter also is obstructed

84. Hyman, A., and Leiter, H. E.: Surgery of the Inferior Vena Cava in Urologic Conditions, J. Urol. **45**:813-826 (June) 1941.

85. Guido, F. R.: Appendiceal Calculus: Report of Case, California & West. Med. **55**:19-22 (July) 1941.

at the point of the shadow, the obstruction being caused by an inflamed appendix adherent to the ureter or by the proximity of the appendical calculus to the ureter.

In Guido's case, the patient was a man aged 38 years. He had not had urinary symptoms; the urine was normal, and there was no pain or tenderness over the right lower quadrant of the abdomen. A roentgenogram revealed a huge calculus in the upper part of the true pelvis at the lower margin of the sacroiliac joint. Intravenous pyelograms did not reveal evidence of dye in the right side. Consequently, a diagnosis of calculus of the lower third of the right ureter was made. The ureter was exposed, but calculus was not seen. The peritoneal cavity was then opened, and calculus was found in the appendix.

In this case, the calculus in the appendix was not typical of ureteral stone. It was large, shaped like a ureteral stone and slightly out of line with the ureter.

RETENTION CATHETER

Owens [86] reports a seemingly essential modification of the bag catheter. In some of the catheters in use at present the bag dilates only on one side of the catheter, commonly causing the catheter to angulate and at times become obstructed. In Owens' modification, the bag enlarges uniformly around the catheter.

86. Owens, C. A.: A Modified Bag Catheter, J. Urol. **46**:344-345 (Aug.) 1941.

CORRECTION

In the article by Dr. Robert Gutierrez, "Large Solitary Cysts of the Kidney: Types, Differential Diagnosis and Surgical Treatment," in the February issue (ARCH. SURG. **44**:279, 1942), the word "laparotomy" in the third line from the bottom of page 314 should read "lumbotomy."